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TLR3-antagonisták

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Description**Field of the Invention**

5 **[0001]** The present invention relates to Toll-Like Receptor 3 (TLR3) antibody antagonists or fragments thereof, and methods of making and using the foregoing.

Background of the Invention

10 **[0002]** Toll-like receptors (TLRs) regulate activation of the innate immune response and influence the development of adaptive immunity by initiating signal transduction cascades in response to bacterial, viral, parasitic, and in some cases, host-derived ligands (Lancaster et al., *J. Physiol.* 563:945-955, 2005). The plasma membrane localized TLRs, TLR1, TLR2, TLR4 and TLR6 recognize ligands including protein or lipid components of bacteria and fungi. The pre-
 15 dominantly intracellular TLRs, TLR3, TLR7 and TLR9 respond to dsRNA, ssRNA and unmethylated CpG DNA, respectively. Dysregulation of TLR signaling is believed to cause a multitude of problems, and therapeutic strategies are in development towards this axis (Hoffman et al., *Nat. Rev. Drug Discov.* 4:879-880, 2005; Rezaei, *Int. Immunopharmacol.* 6:863-869, 2006; Wickelgren, *Science* 312:184-187, 2006). For example, antagonists of TLR4 and TLRs 7 and 9 are in clinical development for severe sepsis and lupus, respectively (Kanzler et al., *Nat. Med.* 13:552-559, 2007).

20 **[0003]** TLR3 signaling is activated by dsRNA, mRNA or RNA released from necrotic cells during inflammation or virus infection. TLR3 activation induces secretion of interferons and pro-inflammatory cytokines and triggers immune cell activation and recruitment that are protective during certain microbial infections. For example, a dominant-negative TLR3 allele has been associated with increased susceptibility to Herpes Simplex encephalitis upon primary infection with HSV-1 in childhood (Zheng et al., *Science* 317:1522-1527 2007). In mice, TLR3 deficiency is associated with
 25 decreased survival upon coxsackie virus challenge (Richer et al., *PLoS One* 4:e4127, 2009). However, uncontrolled or dysregulated TLR3 signaling has been shown to contribute to morbidity and mortality in certain viral infection models including West Nile, phlebovirus, vaccinia, and influenza A (Wang et al., *Nat. Med.* 10:1366-1373, 2004; Gowen et al., *J. Immunol.* 177:6301-6307, 2006; Hutchens et al., *J. Immunol.* 180:483-491, 2008; Le Goffic et al., *PLoS Pathog.* 2:E53, 2006).

30 **[0004]** TLR3 has also been shown to drive pathogenic mechanisms in a spectrum of inflammatory, immune-mediated and autoimmune diseases including, for example, septic shock (Cavassani et al., *J. Exp. Med.* 205:2609-2621, 2008), acute lung injury (Murray et al., *Am. J. Respir. Crit. Care Med.* 178:1227-1237, 2008), rheumatoid arthritis (Kim et al., *Immunol. Lett.* 124:9-17, 2009; Brentano et al., *Arth. Rheum.* 52:2656-2665, 2005), asthma (Sugiura et al., *Am. J. Resp. Cell Mol. Biol.* 40:654-662, 2009; Morishima et al., *Int. Arch. Allergy Immunol.* 145:163-174, 2008; Stowell et al., *Respir. Res.* 10:43, 2009), inflammatory bowel disease such as Crohn's disease and ulcerative colitis (Zhou et al., *J. Immunol.* 178:4548-4556, 2007; Zhou et al., *Proc. Natl. Acad. Sci. (USA)* 104:7512-7515, 2007), autoimmune liver disease (Lang et al., *J. Clin. Invest.* 116:2456-2463, 2006) and type I diabetes (Dogusan et al. *Diabetes* 57:1236-1245, 2008; Lien and Zipris, *Curr. Mol. Med.* 9:52-68, 2009). Furthermore, organ-specific increases in TLR3 expression have been shown to correlate with a number of pathological conditions driven by dysregulated local inflammatory responses such as primary biliary cirrhosis of liver tissues (Takii et al., *Lab Invest.* 85:908-920, 2005), rheumatoid arthritis joints (Ospelt et al.,
 40 *Arthritis Rheum.* 58:3684-3692, 2008), and nasal mucosa of allergic rhinitis patients (Fransson et al., *Respir. Res.* 6:100, 2005).

45 **[0005]** In necrotic conditions, the release of intracellular content including endogenous mRNA triggers secretion of cytokines, chemokines and other factors that induce local inflammation, facilitate clearance of dead cell remnants and repair the damage. Necrosis often perpetuates inflammatory processes, contributing to chronic or exaggerated inflammation (Bergsbaken et al., *Nature Reviews* 7:99-109, 2009). Activation of TLR3 at the site of necrosis may contribute to these aberrant inflammatory processes and generate a further pro-inflammatory positive feedback loop via the released TLR3 ligands. Thus, TLR3 antagonism may be beneficial in a variety of disorders involving chronic or exaggerated inflammation and/or necrosis.

50 **[0006]** Down-modulation of TLR3 activation may also represent a novel treatment strategy for oncologic indications including renal cell carcinomas and head and neck squamous cell carcinomas (Morikawa et al., *Clin. Cancer Res.* 13:5703-5709, 2007; Pries et al., *Int. J. Mol. Med.* 21: 209-215, 2008). Furthermore, the TLR3^{L423F} allele encoding a protein with reduced activity has been associated with protection against advanced "dry" age-related macular degeneration (Yang et al., *N. Engl. J. Med.* 359:1456-1463, 2008), indicating that TLR3 antagonists may be beneficial in this disease.

55 **[0007]** Pathologies associated with inflammatory conditions and others, such as those associated with infections, have significant health and economic impacts. Yet, despite advances in many areas of medicine, comparatively few treatment options and therapies are available for many of these conditions.

[0008] Thus, a need exists to suppress TLR3 activity to treat TLR3-associated conditions.

[0009] US 2006/115475 discusses anti-TLR3 antibodies. Monoclonal antibodies that recognize the extracellular domain of human TLR3 have been described (Duffy et al. Cellular Immunology 248 (2): 103-114, 2007). Agonistic anti-TLR3 antibodies have also been described in US 2007/098716. An anti-TLR3 monoclonal antibody against human TLR3 has been shown to suppress poly(I):poly(C)-mediated IFN- β production by TLR3 expressing human fibroblasts (Matsumoto et al. Biochemical and Biophysical Research Communications 293(5): 1364-1369, 2002 and US 2005/153910).

Brief Description of the Drawings

[0010]

Fig. 1 shows the effect of anti-human TLR3 (huTLR3) mAbs in an NF- κ B reporter gene assay.
 Figs. 2A and 2B show the effect (% inhibition) of anti-huTLR3 mAbs in a BEAS-2B assay.
 Figs. 3A and 3B show the effect of anti-huTLR3 mAbs in a NHBE assay.
 Fig. 4 shows the effect of anti-huTLR3 mAbs in a PBMC assay.
 Figs. 5A and 5B show the effect of anti-huTLR3 mAbs in a HASM assay.
 Figs. 6A, 6B and 6C show the binding of anti-huTLR3 mAbs to TLR3 mutants.
 Fig. 7A shows epitopes for mAb 15EVQ (black) and C1068 mAb (grey) (top image) and epitope for mAb 12QVQ/QSV (black, bottom image) superimposed on the structure of human TLR3 ECD. Fig. 7B shows localized H/D exchange perturbation map of TLR3 ECD protein complexed with mAb 15EVQ.
 Figs. 8A and 8B show the effect of rat/mouse anti-mouse TLR3 mAb mAb 5429 (surrogate) in A) NF- κ B and B) ISRE reporter gene assays.
 Fig. 9 shows the effect of the surrogate mAbs (mAb 5429, mAb c1811) in the MEF CXCL10/IP-10 assay.
 Fig. 10 shows specificity of binding of the surrogate mAb to TLR3. Top panel: isotype control; bottom panel: mAb c1811.
 Fig. 11 shows effect of the surrogate mAbs on penH level in an AHR model.
 Fig. 12 shows effect of the surrogate mAbs on total neutrophil numbers in BAL fluid in an AHR model.
 Fig. 13 shows effect of the surrogate mAbs on CXCL10/IP-10 levels in BAL fluid in an AHR model.
 Fig. 14 shows effect of the surrogate mAb on histopathology scores in a DSS model.
 Fig. 15 shows effect of the surrogate mAb on A) histopathology scores and B) neutrophil influx in a T-cell transfer model.
 Fig. 16 shows effect of the surrogate mAb on clinical scores in a CIA model.
 Fig. 17 shows effect of the surrogate mAb on the clinical AUC scores in a CIA model.
 Fig. 18 shows effect of the surrogate mAb on the survival of C57BL/6 mice following intranasal administration of influenza A/PR/8/34.
 Fig. 19 shows effect of the surrogate mAb on clinical scores following influenza A/PR/8/34 administration.
 Fig. 20 shows effect of the surrogate mAb on body weight over 14 days after administration of influenza A/PR/8/34.
 Fig. 21 shows effect of the surrogate mAbs on blood glucose levels in (A) WT DIO and (B) TLR3KO DIO animals after glucose challenge.
 Fig. 22 shows effect of the surrogate mAb on insulin levels in WT DIO animals.
 Fig. 23 shows effect of mAb 15EVQ on (A) NTHi and (B) rhinovirus induced CXCL10/IP-10 and CCL5/RANTES levels in NHBE cells.
 Fig. 24 shows effect of mAb 15EVQ on (A) sICAM-1 levels and (B) viability in HUVEC cells.

Summary of the Invention

[0011] The first aspect of the invention is an isolated antibody or fragment thereof reactive with toll-like receptor 3 (TLR3), comprising both a heavy chain and a light chain variable region and wherein the antibody comprises:

- a. the heavy chain CDR 1, 2 and 3 amino acid sequences as shown in SEQ ID NO:s 82, 86 and 84; and
- b. the light chain CDR 1, 2 and 3 amino acid sequences as shown in SEQ ID NO:s 79, 80 and 87.

[0012] In one embodiment, the antibody binds at least one TLR3 amino acid residue selected from a group consisting of residues K467, R488, or R489 of SEQ ID NO: 2.

[0013] Also disclosed herein is an isolated antibody or antigen binding fragment thereof, wherein the antibody binds at least one TLR3 amino acid residue selected from a group consisting of residues D116 or K145 of SEQ ID NO: 2.

[0014] In one embodiment the antibody has at least one of the following properties:

- a. reduces human TLR3 biological activity in an *in vitro* poly(I:C) NF- κ B reporter gene assay >50% at <1 μ g/ml;

- b. inhibits >60% of IL-6 or CXCL10/IP-10 production from BEAS-2B cells stimulated with <100 ng/ml poly(I:C) at <10 µg/ml;
- c. inhibits >50% of IL-6 or CXCL10/IP-10 production from BEAS-2B cells stimulated with <100 ng/ml poly(I:C) at <0.4 µg/ml;
- d. inhibits >50% of IL-6 production from NHBE cells stimulated with 62.5 ng/ml poly(I:C) at <5 µg/ml;
- e. inhibits >50% of IL-6 production from NHBE cells stimulated with 62.5 ng/ml poly(I:C) at <1 µg/ml;
- f. inhibits >20% of poly(I:C)-induced IFN-γ, IL-6 or IL-12 production by PBMC cells at <1 µg/ml;
- g. inhibits cynomolgus TLR3 biological activity in an *in vitro* NF-κB reporter gene assay with IC₅₀ <10 µg/ml; or
- h. inhibits cynomolgus TLR3 biological activity in an *in vitro* ISRE reporter gene assay with IC₅₀ <5 µg/ml.

[0015] Also disclosed herein is an isolated antibody reactive with TLR3 that competes for TLR3 binding with a monoclonal antibody, wherein the monoclonal antibody comprises the amino acid sequences of heavy chain complementarity determining regions (CDRs) 1, 2 and 3 as shown in SEQ ID NOs: 82, 86 and 84, and the amino acid sequences of light chain CDRs 1, 2 and 3, as shown in SEQ ID NOs: 79, 80 and 87, or wherein the monoclonal antibody comprises the amino acid sequence of heavy chain variable region (VH), as shown in SEQ ID NO: 216 and the amino acid sequence of light chain variable region (VL), as shown in SEQ ID NO: 41.

[0016] Also disclosed herein is an isolated antibody reactive with TLR3 comprising both a heavy chain and a light chain variable region and wherein the antibody comprises certain heavy chain complementarity determining regions (CDRs) 1, 2 and 3 and the amino acid sequences of certain light chain CDRs 1, 2 and 3.

[0017] Also disclosed herein is an isolated antibody reactive with TLR3 comprising both a heavy chain and a light chain variable region and wherein the antibody comprises the amino acid sequences of certain heavy chain variable regions (VH) and the amino acid sequences of certain light chain variable regions (VL).

[0018] Also disclosed herein is an isolated antibody reactive with TLR3 comprising both a heavy chain and a light chain variable region and wherein the antibody comprises the amino acid sequence of certain heavy chain and the amino acid sequence of certain light chain.

[0019] Also disclosed herein is an isolated antibody heavy chain comprising the amino acid sequence shown in SEQ ID NO: 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 124, 125, 126, 127, 128, 129, 159, 198, 200, 202, 164, 212, 213, 214, 215 or 216.

[0020] Also disclosed herein is an isolated antibody light chain comprising the amino acid sequence shown in SEQ ID NO: 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 122, 123, 197, 199, 201, 163, 209, 210 or 211.

[0021] Also disclosed herein is an isolated antibody heavy chain comprising the amino acid sequence shown in SEQ ID NO: 102, 130, 131, 132, 133, 134, 135, 160, 204, 206, 208, 220, 166 or 168.

[0022] Also disclosed herein is an isolated antibody light chain comprising the amino acid sequence shown in SEQ ID NO: 155, 156, 157, 158, 203, 205, 207, 165 or 167.

[0023] Also disclosed herein is an isolated polynucleotide encoding an antibody heavy chain comprising the amino acid sequence shown in SEQ ID NO: 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 124, 125, 126, 127, 128, 129, 159, 198, 200, 202, 164, 212, 213, 214, 215 or 216.

[0024] Also disclosed herein is an isolated polynucleotide encoding an antibody light chain comprising the amino acid sequence shown in SEQ ID NO: 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 122, 123, 197, 199, 201, 163, 209, 210 or 211.

[0025] Also disclosed herein is an isolated polynucleotide encoding an antibody heavy chain comprising the amino acid sequence shown in SEQ ID NO: 102, 130, 131, 132, 133, 134, 135, 160, 204, 206, 208, 220, 166 or 168.

[0026] Also disclosed herein is an isolated polynucleotide encoding an antibody light chain comprising the amino acid sequence shown in SEQ ID NO: 155, 156, 157, 158, 203, 205, 207, 165 or 167.

[0027] Another aspect of the invention is a pharmaceutical composition comprising the isolated antibody of the invention and a pharmaceutically acceptable carrier. Also disclosed herein is a vector comprising at least one polynucleotide herein disclosed.

[0028] Also disclosed herein is a host cell comprising the vector of the invention.

[0029] Also disclosed herein is a method of making an antibody reactive with TLR3 according to claim 1 comprising culturing the host cell disclosed herein and recovering the antibody produced by the host cell.

[0030] Another aspect of the invention is the isolated antibody or pharmaceutical composition of the invention for use in therapy.

[0031] In one embodiment the isolated antibody or pharmaceutical composition of the invention is for use in a method of treating or preventing an inflammatory condition comprising administering a therapeutically effective amount of the isolated antibody or the pharmaceutical composition of the invention to a patient in need thereof for a time sufficient to treat or prevent the inflammatory condition.

[0032] In one embodiment the isolated antibody or pharmaceutical composition of the invention is for use in a method of treating or preventing a systemic inflammatory condition comprising administering a therapeutically effective amount

of the isolated antibody or the pharmaceutical composition of the invention to a patient in need thereof for a time sufficient to treat or prevent the systemic inflammatory condition.

[0033] In one embodiment the isolated antibody or pharmaceutical composition of the invention is for use in a method of treating type II diabetes comprising administering a therapeutically effective amount of the isolated antibody or the pharmaceutical composition of the invention to a patient in need thereof for a time sufficient to treat type II diabetes.

[0034] In one embodiment the isolated antibody or pharmaceutical composition of the invention is for use in a method of treating hyperglycemia comprising administering a therapeutically effective amount of the isolated antibody or the pharmaceutical composition of the invention to a patient in need thereof for a time sufficient to treat the hyperglycemia.

[0035] In one embodiment the isolated antibody or pharmaceutical composition of the invention is for use in a method of treating hyperinsulinemia comprising administering a therapeutically effective amount of the isolated antibody or the pharmaceutical composition of the invention to a patient in need thereof for a time sufficient to treat the insulin resistance.

[0036] In one embodiment the isolated antibody or pharmaceutical composition of the invention is for use in a method of treating or preventing viral infections comprising administering a therapeutically effective amount of the isolated antibody or the pharmaceutical composition of the invention to a patient in need thereof for a time sufficient to treat or prevent viral infections.

Detailed Description of the Invention

[0037] The term "antagonist" as used herein means a molecule that partially or completely inhibits, by any mechanism, an effect of another molecule such as a receptor or intracellular mediator.

[0038] As used herein, a "TRL3 antibody antagonist" or an antibody "reactive with TLR3" describes an antibody that is capable of, directly or indirectly, substantially counteracting, reducing or inhibiting TLR3 biological activity or TLR3 receptor activation. For example, an antibody reactive with TLR3 can bind directly to TLR3 and neutralize TLR3 activity, i.e. block TLR3 signaling to reduce cytokine and chemokine release or NF- κ B activation.

[0039] The term "antibodies" as used herein is meant in a broad sense and includes immunoglobulin or antibody molecules including polyclonal antibodies, monoclonal antibodies including murine, human, human-adapted, humanized and chimeric monoclonal antibodies and antibody fragments.

[0040] In general, antibodies are proteins or peptide chains that exhibit binding specificity to a specific antigen. Intact antibodies are heterotetrameric glycoproteins, composed of two identical light chains and two identical heavy chains. Typically, each light chain is linked to a heavy chain by one covalent disulfide bond, while the number of disulfide linkages varies between the heavy chains of different immunoglobulin isotypes. Each heavy and light chain also has regularly spaced intrachain disulfide bridges. Each heavy chain has at one end a variable domain (VH) followed by a number of constant domains. Each light chain has a variable domain at one end (VL) and a constant domain at its other end; the constant domain of the light chain is aligned with the first constant domain of the heavy chain and the light chain variable domain is aligned with the variable domain of the heavy chain. Antibody light chains of any vertebrate species can be assigned to one of two clearly distinct types, namely kappa (κ) and lambda (λ), based on the amino acid sequences of their constant domains.

[0041] Immunoglobulins can be assigned to five major classes, namely IgA, IgD, IgE, IgG and IgM, depending on the heavy chain constant domain amino acid sequence. IgA and IgG are further sub-classified as the isotypes IgA₁, IgA₂, IgG₁, IgG₂, IgG₃ and IgG₄.

[0042] The term "antibody fragments" means a portion of an intact antibody, generally the antigen binding or variable region of the intact antibody. Examples of antibody fragments include Fab, Fab', F(ab')₂ and Fv fragments, diabodies, single chain antibody molecules and multispecific antibodies formed from at least two intact antibodies.

[0043] An immunoglobulin light or heavy chain variable region consists of a "framework" region interrupted by three "antigen-binding sites". The antigen-binding sites are defined using various terms as follows: (i) the term Complementarity Determining Regions (CDRs) is based on sequence variability (Wu and Kabat, J. Exp. Med. 132:211-250, 1970). Generally, the antigen-binding site has six CDRs; three in the VH (HCDR1, HCDR2, HCDR3), and three in the VL (LCDR1, LCDR2, LCDR3) (Kabat et al., Sequences of Proteins of Immunological Interest, 5th Ed. Public Health Service, National Institutes of Health, Bethesda, Md., 1991). (ii) The term "hypervariable region", "HVR", or "HV" refers to the regions of an antibody variable domain which are hypervariable in structure as defined by Chothia and Lesk (Chothia and Lesk, Mol. Biol. 196:901-917, 1987). Generally, the antigen-binding site has six hypervariable regions, three in VH (H1, H2, H3) and three in VL (L1, L2, L3). Chothia and Lesk refer to structurally conserved HVs as "canonical structures". (iii) The "IMGT-CDRs" as proposed by Lefranc (Lefranc et al., Dev. Comparat. Immunol. 27:55-77, 2003) are based on the comparison of V domains from immunoglobulins and T-cell receptors. The International ImMunoGeneTics (IMGT) database (<http://www.imgt.org>) provides a standardized numbering and definition of these regions. The correspondence between CDRs, HVs and IMGT delineations is described in Lefranc et al., Dev. Comparat. Immunol. 27:55-77, 2003. (iv) The antigen-binding site can also be delineated based on Specificity Determining Residue Usage (SDRU), according to Almagro (Almagro, Mol. Recognit. 17:132-143, 2004), where Specificity Determining Residues (SDR), refers to amino

acid residues of an immunoglobulin that are directly involved in antigen contact. SDRU as defined by Almargo is a precise measure of a number and distribution of SDR for different types of antigens as defined by analyses of crystal structures of antigen-antibody complexes.

[0044] The term "composite sequences" as used herein means an antigen-binding site defined to include all amino acid residues delineated individually by Kabat, Chothia or IMGT, or any other suitable antigen-binding region delineation.

[0045] "Framework" or "framework sequences" are the remaining sequences of a variable region other than those defined to be antigen-binding site. Because the antigen-binding site can be defined by various terms as described above, the exact amino acid sequence of a framework depends on how the antigen-binding site was defined.

[0046] The term "antigen" as used herein means any molecule that has the ability to generate antibodies either directly or indirectly. Included within the definition of "antigen" is a protein-encoding nucleic acid.

[0047] The term "homolog" means protein sequences having between 40% and 100% sequence identity to a reference sequence. Homologs of human TLR3 include polypeptides from other species that have between 40% and 100% sequence identity to a known human TLR3 sequence. Percent identity between two peptide chains can be determined by pairwise alignment using the default settings of the AlignX module of Vector NTI v.9.0.0 (Invitrogen, Carlsbad, CA). By "TLR3" is meant human TLR3 (huTLR3) and its homologs. The nucleotide and amino acid sequences of the full length huTLR3 are shown in SEQ ID NOS: 1 and 2, respectively. The nucleotide and amino acid sequences of the huTLR3 extracellular domain (ECD) are shown in SEQ ID NOS: 3 and 4, respectively.

[0048] The term "substantially identical" as used herein means that the two antibody or antibody fragment amino acid sequences being compared are identical or have "insubstantial differences". Insubstantial differences are substitutions of 1, 2, 3, 4, 5 or 6 amino acids in an antibody or antibody fragment amino acid sequence. Amino acid sequences substantially identical to the sequences disclosed herein are also part of this application. In some embodiments, the sequence identity can be about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or higher. Percent identity can be determined as described above. Exemplary peptide chains being compared are heavy or light chain variable regions.

[0049] The term "in combination with" as used herein means that the described agents can be administered to an animal together in a mixture, concurrently as single agents or sequentially as single agents in any order.

[0050] The term "inflammatory condition" as used herein means a localized response to cellular injury that is mediated in part by the activity of cytokines, chemokines, or inflammatory cells (e.g., neutrophils, monocytes, lymphocytes, macrophages) which is characterized in most instances by pain, redness, swelling, and loss of tissue function. The term "inflammatory pulmonary condition" as used herein means an inflammatory condition affecting or associated with the lungs.

[0051] The term "monoclonal antibody" (mAb) as used herein means an antibody (or antibody fragment) obtained from a population of substantially homogeneous antibodies. Monoclonal antibodies are highly specific, typically being directed against a single antigenic determinant. The modifier "monoclonal" indicates the substantially homogeneous character of the antibody and does not require production of the antibody by any particular method. For example, murine mAbs can be made by the hybridoma method of Kohler et al., *Nature* 256:495-497, 1975. Chimeric mAbs containing a light chain and heavy chain variable region derived from a donor antibody (typically murine) in association with light and heavy chain constant regions derived from an acceptor antibody (typically another mammalian species such as human) can be prepared by the method disclosed in U.S. Pat. No. 4,816,567. Human-adapted mAbs having CDRs derived from a non-human donor immunoglobulin (typically murine) and the remaining immunoglobulin-derived parts of the molecule being derived from one or more human immunoglobulins can be prepared by techniques known to those skilled in the art such as that disclosed in U.S. Pat. No. 5,225,539. Human framework sequences useful for human-adaptation can be selected from relevant databases by those skilled in the art. Optionally, human-adapted mAbs can be further modified by incorporating altered framework support residues to preserve binding affinity by techniques such as those disclosed in Queen et al., *Proc. Natl. Acad. Sci. (USA)*, 86:10029-10032, 1989 and Hodgson et al., *Bio/Technology*, 9:421, 1991.

[0052] Fully human mAbs lacking any non-human sequences can be prepared from human immunoglobulin transgenic mice by techniques referenced in, e.g., Lonberg et al., *Nature* 368:856-859, 1994; Fishwild et al., *Nature Biotechnology* 14:845-851, 1996; and Mendez et al., *Nature Genetics* 15:146-156, 1997. Human mAbs can also be prepared and optimized from phage display libraries by techniques referenced in, e.g., Knappik et al., *J. Mol. Biol.* 296:57-86, 2000; and Krebs et al., *J. Immunol. Meth.* 254:67-84 2001.

[0053] The term "epitope" as used herein means a portion of an antigen to which an antibody specifically binds. Epitopes usually consist of chemically active (such as polar, nonpolar or hydrophobic) surface groupings of moieties such as amino acids or polysaccharide side chains and can have specific three-dimensional structural characteristics, as well as specific charge characteristics. An epitope can be linear in nature or can be a discontinuous epitope, e.g., a conformational epitope, which is formed by a spatial relationship between non-contiguous amino acids of an antigen rather than a linear series of amino acids. A conformational epitope includes epitopes resulting from folding of an antigen, where amino acids from differing portions of the linear sequence of the antigen come in close proximity in 3-dimensional space.

[0054] The term "specific binding" as used herein refers to antibody binding to a predetermined antigen with greater

affinity than for other antigens or proteins. Typically, the antibody binds with a dissociation constant (K_D) of 10^{-7} M or less, and binds to the predetermined antigen with a K_D that is at least twofold less than its K_D for binding to a nonspecific antigen (e.g., BSA, casein, or any other specified polypeptide) other than the predetermined antigen. The phrases "an antibody recognizing an antigen" and "an antibody specific for an antigen" are used interchangeably herein with the term "an antibody which binds specifically to an antigen" or "an antigen specific antibody" e.g. a TLR3 specific antibody. The dissociation constant can be measured using standard procedures as described below.

[0055] The term "TLR3 biological activity" or "TLR3 activation" as used herein refers to any activity occurring as a result of ligand binding to TLR3. TLR3 ligands include dsRNA, poly(I:C), and endogenous mRNA, e.g., endogenous mRNA released from necrotic cells. An exemplary TLR3 activation results in activation of NF- κ B in response to the TLR3 ligand. NF- κ B activation can be assayed using a reporter-gene assay upon induction of the receptor with poly(I:C) (Alexopoulou et al., Nature 413:732-738, 2001; Hacker et al., EMBO J. 18:6973-6982, 1999). Another exemplary TLR3 activation results in activation of interferon response factors (IRF-3, IRF-7) in response to TLR3 ligand. TLR3-mediated IRF activation can be assayed using a reporter gene driven by an interferon-stimulated response element (ISRE). Another exemplary TLR3 activation results in secretion of pro-inflammatory cytokines and chemokines, for example TNF- α , IL-6, IL-8, IL-12, CXCL5/IP-10 and RANTES. The release of cytokines and chemokines from cells, tissues or in circulation can be measured using well-known immunoassays, such as an ELISA immunoassay.

[0056] Conventional one and three-letter amino acid codes are used herein as follows:

	Amino acid	Three-letter code	One-letter code
20	Alanine	ala	A
	Arginine	arg	R
	Asparagine	asn	N
	Aspartate	asp	D
25	Cysteine	cys	C
	Glutamate	glu	E
	Glutamine	gln	Q
	Glycine	gly	G
	Histidine	his	H
30	Isoleucine	ile	I
	Leucine	leu	L
	Lysine	lys	K
	Methionine	met	M
35	Phenylalanine	phe	F
	Proline	pro	P
	Serine	ser	S
	Threonine	thr	T
	Tryptophan	trp	W
40	Tyrosine	tyr	Y
	Valine	val	V

Compositions of matter

[0057] The present invention provides antibody antagonists capable of inhibiting TLR3 biological activity and uses of such antibodies as defined in the claims. Such TLR3 antagonists may have the properties of binding TLR3 and inhibiting TLR3 activation. Exemplary mechanisms by which TLR3 activation may be inhibited by such antibodies include *in vitro*, *in vivo* or *in situ* inhibition of ligand binding to TLR3, inhibition of receptor dimerization, inhibition of TLR3 localization to the endosomal compartment, inhibition of kinase activity of downstream signaling pathways, or inhibition of TLR3 mRNA transcription. Other antibody antagonists capable of inhibiting TLR3 activation by other mechanisms are also within the scope of the various aspects and embodiments of the invention. These antagonists are useful as research reagents, diagnostic reagents and therapeutic agents.

[0058] Antibody diversity is created by use of multiple germline genes encoding variable regions and a variety of somatic events. The somatic events include recombination of variable (V) gene segments and diversity (D) and joining (J) gene segments to make a complete VH region and the recombination of variable and joining gene segments to make a complete VL region. Antibodies and compositions having identical or similar CDR sequence to those disclosed herein are not likely to have been independently generated. The sequence of antibody genes after assembly and somatic

mutation is highly varied, and these varied genes are estimated to encode 10^{10} different antibody molecules (Immunoglobulin Genes, 2nd ed., eds. Jonio et al., Academic Press, San Diego, Calif., 1995).

[0059] The invention provides novel antigen-binding sites derived from human immunoglobulin gene libraries. The structure for carrying an antigen-binding site is generally an antibody heavy or light chain or portion thereof, where the antigen-binding site is located to a naturally occurring antigen-binding site as determined as described above.

[0060] The invention provides an isolated antibody or fragment thereof reactive with TLR3 as recited in claim 1 comprising both a heavy chain and a light chain variable region and wherein the antibody comprises the heavy chain complementarity determining regions (CDR) amino acid sequences 1, 2 and 3 (HCDR1, HCDR2 and HCDR3), as shown in SEQ ID NOs: 82, 86 and 84 and the light chain complementarity determining regions (CDR) amino acid sequences 1, 2 and 3 (LCDR1, LCDR2 and LCDR3) SEQ ID NOs: 79, 80 and 87, as shown in Table 1a.

[0061] Also disclosed are other antibodies or fragments thereof reactive with TLR3 comprising both a heavy chain and a light chain variable region and wherein the antibody comprises the heavy chain complementarity determining regions (CDR) amino acid sequences 1, 2 and 3 (HCDR1, HCDR2 and HCDR3) and the light chain complementarity determining regions (CDR) amino acid sequences 1, 2 and 3 (LCDR1, LCDR2 and LCDR3) as shown in Table 1a.

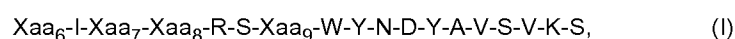
Table 1a.

mAb	SEQ ID NO:					
	HCDR1	HCDR2	HCDR3	LCDR1	LCDR2	LCDR3
16	52	88	54	49	50	51
17	58	64	60	55	56	57
18	70	77	72	67	68	69
19	82	83	84	79	80	89
1	46	47	48	43	44	45
2	52	53	54	49	50	51
3	58	59	60	55	56	57
4	61	62	60	55	56	57
5	61	64	60	55	56	63
6	61	64	60	55	56	65
7	61	64	60	55	56	66
8	70	71	72	67	68	69
9	70	73	72	67	68	69
10	70	75	72	67	68	74
11	70	77	72	67	68	76
12	70	77	72	67	68	78
13	82	83	84	79	80	81
14	82	86	84	79	80	85
15*	82	86	84	79	80	87
15**	111	112	84	109	110	113
15-1	111	114	84	109	110	113
15-2	115	112	84	109	110	113
15-3	116	112	84	109	110	113
15-4	111	117	84	109	110	113
15-5	116	118	84	109	110	113
15-6	116	112	119	109	110	113
15-7	111	112	84	120	110	113

(continued)

mAb	SEQ ID NO:					
	HCDR1	HCDR2	HCDR3	LCDR1	LCDR2	LCDR3
15-8	111	112	84	121	110	113
15-9	116	118	119	109	110	113
F17	61	192	60	55	56	191
F18	70	194	72	67	68	193
F19	82	196	84	79	80	195

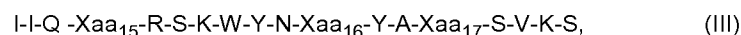
[0062] Disclosed herein is an isolated antibody or fragment reactive with TLR3 comprising both a heavy chain and a light chain variable region and wherein the antibody comprises a HCDR2 amino acid sequence as shown in SEQ ID NO: 192, wherein the HCDR2 of SEQ ID NO: 192 is defined as shown in Formula (I) :



wherein

Xaa₆ may be Arg or Lys;
 Xaa₇ may be Tyr, His or Ser;
 Xaa₈ may be Met, Arg or Tyr; and
 Xaa₉ may be Lys or Arg.

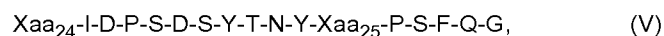
[0063] Also disclosed herein is an isolated antibody or fragment reactive with TLR3 comprising both a heavy chain and a light chain variable region and wherein the antibody comprises a HCDR2 amino acid sequence as shown in SEQ ID NO: 194, wherein the HCDR2 of SEQ ID NO: 194 is defined as shown in Formula (III):



wherein

Xaa₁₅ may be Lys, Thr or Ile;
 Xaa₁₆ may be Asn or Asp; and
 Xaa₁₇ may be Val or Leu.

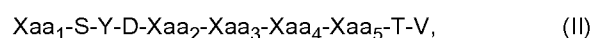
[0064] Also disclosed herein is an isolated antibody or fragment reactive with TLR3 comprising both a heavy chain and a light chain variable region and wherein the antibody comprises a HCDR2 amino acid sequence as shown in SEQ ID NO: 196, wherein the HCDR2 of SEQ ID NO: 196 is defined as shown in Formula (V):



wherein

Xaa₂₄ may be Phe or Arg; and
 Xaa₂₅ may be Ala or Ser.

[0065] Also disclosed herein is an isolated antibody or fragment reactive with TLR3 comprising both a heavy chain and a light chain variable region and wherein the antibody comprises a LCDR3 amino acid sequence as shown in SEQ ID NO: 191, wherein the LCDR3 of SEQ ID NO: 191 is defined as shown in Formula (II):



wherein

Xaa₁ may be Ala, Gln, Gly or Ser;

Xaa₂ may be Gly, Glu or Ser;
 Xaa₃ may be Asp or Asn;
 Xaa₄ may be Glu or Ser; and
 Xaa₅ may be Phe, Ala or Leu.

[0066] Also disclosed herein is an isolated antibody or fragment reactive with TLR3 comprising both a heavy chain and a light chain variable region and wherein the antibody comprises a LCDR3 amino acid sequence as shown in SEQ ID NO: 193, wherein the LCDR3 of SEQ ID NO: 193 is defined as shown in Formula (IV):

Xaa₁₀-S-Y-D-Xaa₁₁-P-Xaa₁₂-Xaa₁₃-Xaa₁₄-V, (IV)

wherein

Xaa₁₀ may be Gln or Ser;
 Xaa₁₁ may be Thr, Glu or Asp;
 Xaa₁₂ may be Val or Asn;
 Xaa₁₃ may be Tyr or Phe; and
 Xaa₁₄ may be Ser, Asn or Gln.

[0067] Also disclosed herein is an isolated antibody or fragment reactive with TLR3 comprising both a heavy chain and a light chain variable region and wherein the antibody comprises a LCDR3 amino acid sequence as shown in SEQ ID NO: 195, wherein the LCDR3 of SEQ ID NO: 195 is defined as shown in Formula (VI):

Q-Q-Xaa₁₈-Xaa₁₉-Xaa₂₀-Xaa₂₁-Xaa₂₂-Xaa₂₃-T, (VI)

wherein

Xaa₁₈ may be Tyr, Gly or Ala;
 Xaa₁₉ may be Gly, Glu or Asn;
 Xaa₂₀ may be Ser or Thr;
 Xaa₂₁ may be Val, Ile or Leu;
 Xaa₂₂ may be Ser or Leu; and
 Xaa₂₃ may be Ile, Ser, Pro or Tyr.

[0068] Also disclosed herein are other isolated antibodies or fragments reactive with TLR3 having the heavy chain complementarity determining regions (CDR) amino acid sequences 1,2 and 3 (HCDR1, HCDR2 and HCDR3) and light chain complementarity determining regions (CDR) amino acid sequences 1, 2 and 3 (LCDR1, LCDR2 and LCDR3) as shown in Table 1a.

[0069] Antibodies whose antigen-binding site amino acid sequences differ insubstantially from those shown in Table 1a (SEQ ID NOs: 49-121 and 191-196) are also disclosed. Typically, this involves one or more amino acid substitutions with an amino acid having similar charge, hydrophobic, or stereochemical characteristics. Additional substitutions in the framework regions, in contrast to antigen-binding sites may also be made as long as they do not adversely affect the properties of the antibody. Substitutions may be made to improve antibody properties, for example stability or affinity. One, two, three, four, five or six substitutions can be made to the antigen binding site.

[0070] Conservative modifications will produce molecules having functional and chemical characteristics similar to those of the molecule from which such modifications are made. Substantial modifications in the functional and/or chemical characteristics of the molecules may be accomplished by selecting substitutions in the amino acid sequence that differ significantly in their effect on maintaining (1) the structure of the molecular backbone in the area of the substitution, for example, as a sheet or helical conformation, (2) the charge or hydrophobicity of the molecule at the target site, or (3) the size of the molecule. For example, a "conservative amino acid substitution" may involve a substitution of a native amino acid residue with a nonnative residue such that there is little or no effect on the polarity or charge of the amino acid residue at that position. Furthermore, any native residue in the polypeptide may also be substituted with alanine, as has been previously described for alanine scanning mutagenesis (MacLennan et al., Acta Physiol. Scand. Suppl. 643:55-67, 1998; Sasaki et al., Adv. Biophys. 35:1-24, 1998). Desired amino acid substitutions (whether conservative or non-conservative) can be determined by those skilled in the art at the time such substitutions are desired. For example, amino acid substitutions can be used to identify important residues of the molecule sequence, or to increase or decrease the affinity of the molecules described herein. Exemplary amino acid substitutions are shown in Table 1b.

Table 1b.

Original residue	Exemplary substitutions	More Conservative substitutions
Ala (A)	Val, Leu, Ile	Val
Arg (R)	Lys, Gln, Asn	Lys
Asn (N)	Gln	Gln
Asp (D)	Glu	Glu
Cys (C)	Ser, Ala	Ser
Gln (Q)	Asn	Asn
Gly (G)	Pro, Ala	Ala
His (H)	Asn, Gln, Lys, Arg	Arg
Ile (I)	Leu, Val, Met, Ala, Phe, Norleucine	Leu
Leu (L)	Norleucine, Ile, Val, Met, Ala, Phe	Ile
Lys (K)	Arg, 1, 4 Diamino-butyric Acid, Gln, Asn	Arg
Met (M)	Leu, Phe, Ile	Leu
Phe (F)	Leu, Val, Ile, Ala, Tyr	Leu
Pro (P)	Ala	Gly
Ser (S)	Thr, Ala, Cys	Thr
Thr (T)	Ser	Ser
Trp (W)	Tyr, Phe	Tyr
Tyr (Y)	Trp, Phe, Thr, Ser	Phe
Val (V)	Ile, Met, Leu, Phe, Ala, Norleucine	Leu

[0071] In certain embodiments, conservative amino acid substitutions also encompass non-naturally occurring amino acid residues which are typically incorporated by chemical peptide synthesis rather than by synthesis in biological systems. Amino acid substitutions can be done for example by PCR mutagenesis (US Pat. No. 4,683,195). Libraries of variants can be generated using well known methods, for example using random (NNK) or non-random codons, for example DKK codons, which encode 11 amino acids (ACDEGKNRSYW), and screening the libraries for variants with desired properties, as shown in Example 1. Table 1c shows substitutions made to three parent TLR3 antibody antagonists within the LCDR3 and HCDR2 regions to improve antibody properties.

[0072] Depending on delineation of the antigen-binding sites, the antigen-binding site residues of the antibodies of the invention and subsequently the framework residues may vary slightly for each heavy and light chain. Table 2a and 2b shows the antigen-binding site residues of exemplary antibodies of the invention delineated according to Kabat, Chothia and IMGT, and their composite sequences.

[0073] Another exemplary antibody of the disclosure (mAb 14) is similarly shown in Tables 2a and 2b.

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Table 1c.

Family 17	LCDR3											SEQ ID NO:
mAb												
17	A	S	Y	D	G	D	E	F	T	V		
3												
4												
5	Q				E		S	A				
6	G				S	N	S	L				
7	S				S		S	L				
consensus	A,Q,G,S	S	Y	D	G,E,S	D,N	E,S	F,A,L	T	V	191	

Family 17	HCDR2																		SEQ ID NO:
mAb																			
17	R	I	Y	M	R	S	K	W	Y	N	D	Y	A	V	S	V	K	S	
3			H	R															
4	K		S	Y			R												
5																			
6																			
7																			
consensus	R,K	I	Y,H,S	M,R,Y	R	S	K,R	W	Y	N	D	Y	A	V	S	V	K	S	192

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Family 18A	LCDR3											SEQ ID NO:
mAb												
18	Q	S	Y	D	S	Q	F	S	F	G	V	
8												
9												
Family 18B												
mAb												
10	Q	S	Y	D	T	P	V	Y	S	V		
11	S				E		N	F	N			
12	S				D		N	F	Q			
consensus	Q,S	S	Y	D	T,E,D	P	V,N	Y,F	S,N,Q	V		193

*consensus based on mAbs 10, 11, 12

Family 18A, 18B	HCDR2																	SEQ ID NO:
mAb																		
18	I	I	Q	K	R	S	K	W	Y	N	N	Y	A	V	S	V	K	S
8				T							D							
9				I							D			L				
10																		
11																		
12																		
consensus	I	I	Q	K,T,I	R	S	K	W	Y	N	N,D	Y	A	V,L	S	V	K	S

Family 19	LCDR2										SEQ ID NO:
mAb											
19	Q	Q	Y	G	S	V	S	I	T		
13			G	E	S	I	L	S			
14			A	E	T			P			
15			G	N	T	L		Y			
15-1			G	N	T	L		Y			
15-2			G	N	T	L		Y			
15-3			G	N	T	L		Y			
15-4			G	N	T	L		Y			
15-5			G	N	T	L		Y			
15-6			G	N	T	L		Y			
15-7			G	N	T	L		Y			
15-8			G	N	T	L		Y			
15-9			G	N	T	L		Y			
consensus	Q	Q	Y,G,A	G,E,N	S,T	V,I,L	S,L	I,S,P,Y	T		195

Family 19	HCDR2																	SEQ ID NO:
mAb																		
19	F	I	D	P	S	D	S	Y	T	N	Y	A	P	S	F	Q	G	
13																		
14																		
15																		
15.1	R																	
15.2																		
15.3																		
15.4												S						
15.5	R											S						
15.6																		
15.7																		
15-8																		
15-9	R											S						
consensus	F,R	I	D	P	S	D	S	Y	T	N	Y	A,S	P	S	F	Q	G	196

Table 2a.

mAb	CDR definition	HCDR1		HCDR2		HCDR3	
		SEQ ID	Sequence	SEQ ID	Sequence	SEQ ID	Sequence
14	IMGT	82	GYSFTNYW	86	IDPDSYTN	84	ARELYQGYMDTFDS
14	Kabat		NYWVG		FIDPDSYTN		ELYQGYMDTFDS
14	Chothia		GYSFT		PSDSYT		LYQGYMDTFD
14	Consensus	111	GYSFTNYWVG	112	FIDPDSYTN	84	ARELYQGYMDTFDS
15	IMGT	82	GYSFTNYW	86	IDPDSYTN	84	ARELYQGYMDTFDS
15	Kabat		NYWVG		FIDPDSYTN		ELYQGYMDTFDS
15	Chothia		GYSFT		PSDSYT		LYQGYMDTFD
15	Consensus	111	GYSFTNYWVG	112	FIDPDSYTN	84	ARELYQGYMDTFDS
15-1	IMGT	82	GYSFTNYW	86	IDPDSYTN	84	ARELYQGYMDTFDS
15-1	Kabat		NYWVG		RIDPDSYTN		ELYQGYMDTFDS
15-1	Chothia		GYSFT		PSDSYT		LYQGYMDTFD
15-1	Consensus	111	GYSFTNYWVG	114	RIDPDSYTN	84	ARELYQGYMDTFDS
15-2	IMGT	82	GYSFTNYW	86	IDPDSYTN	84	ARELYQGYMDTFDS
15-2	Kabat		NYWIG		FIDPDSYTN		ELYQGYMDTFDS
15-2	Chothia		GYSFT		PSDSYT		LYQGYMDTFD
15-2	Consensus	115	GYSFTNYWIG	112	FIDPDSYTN	84	ARELYQGYMDTFDS
15-3	IMGT	82	GYSFTNYW	86	IDPDSYTN	84	ARELYQGYMDTFDS
15-3	Kabat		NYWIS		FIDPDSYTN		ELYQGYMDTFDS
15-3	Chothia		GYSFT		PSDSYT		LYQGYMDTFD
15-3	Consensus	116	GYSFTNYWIS	112	FIDPDSYTN	84	ARELYQGYMDTFDS
15-4	IMGT	82	GYSFTNYW	86	IDPDSYTN	84	ARELYQGYMDTFDS
15-4	Kabat		NYWVG		FIDPDSYTN		ELYQGYMDTFDS
15-4	Chothia		GYSFT		PSDSYT		LYQGYMDTFD
15-4	Consensus	111	GYSFTNYWVG	117	FIDPDSYTN	84	ARELYQGYMDTFDS

(continued)

mAb	CDR definition	HCDR1		HCDR2		HCDR3	
		SEQ ID	Sequence	SEQ ID	Sequence	SEQ ID	Sequence
15-5	IMGT	82	GYSFTNYW	86	IDPDSYNTNY	84	ARELYQGYMDTFDS
15-5	Kabat		NYWIS		RIDPDSYNTNYSPSFQ		ELYQGYMDTFDS
15-5	Chothia		GYSFT		PSDSYT		LYQGYMDTFD
15-5	Consensus	116	GYSFTNYWIS	118	RIDPDSYNTNYSPSFQ	84	ARELYQGYMDTFDS
15-6	IMGT	82	GYSFTNYW	86	IDPDSYNTNY		ARQLYQGYMDTFDS
15-6	Kabat		NYWIS		FIDPDSYNTNYAPSFQ		QLYQGYMDTFDS
15-6	Chothia		GYSFT		PSDSYT		LYQGYMDTFD
15-6	Consensus	116	GYSFTNYWIS	112	FIDPDSYNTNYAPSFQ	119	ARQLYQGYMDTFDS
15-7	IMGT	82	GYSFTNYW	86	IDPDSYNTNY	84	ARELYQGYMDTFDS
15-7	Kabat		NYWVG		FIDPDSYNTNYAPSFQ		ELYQGYMDTFDS
15-7	Chothia		GYSFT		PSDSYT		LYQGYMDTFD
15-7	Consensus	111	GYSFTNYWVG	112	FIDPDSYNTNYAPSFQ	84	ARELYQGYMDTFDS
15-8	IMGT	82	GYSFTNYW	86	IDPDSYNTNY	84	ARELYQGYMDTFDS
15-8	Kabat		NYWVG		FIDPDSYNTNYAPSFQ		ELYQGYMDTFDS
15-8	Chothia		GYSFT		PSDSYT		LYQGYMDTFD
15-8	Consensus	111	GYSFTNYWVG	112	FIDPDSYNTNYAPSFQ	84	ARELYQGYMDTFDS
15-9	IMGT	82	GYSFTNYW	86	IDPDSYNTNY	119	AROLYQGYMDTFDS
15-9	Kabat		NYWIS		RIDPDSYNTNYSPSFQ		QLYQGYMDTFDS
15-9	Chothia		GYSFT		PSDSYT		LYQGYMDTFD
15-9	Consensus	116	GYSFTNYWIS	118	RIDPDSYNTNYSPSFQ	119	ARQLYQGYMDTFDS

[0074] In other embodiments, the invention provides an isolated antibody or fragment reactive with TLR3 according to claim 1 comprising both a heavy chain and a light chain variable region wherein the antibody comprises the amino acid sequences of the heavy chain variable (VH) and the light chain variable (VL) regions as shown in Table 3a. F17, F18 and F19 represent antibody variants comprising consensus amino acid sequences for families 17, 18 and 19, respectively (see Example 1).

[0075] In some embodiments, the invention provides an isolated antibody or fragment thereof reactive with TLR3 comprising both a heavy chain and a light chain variable region and wherein the antibody comprises the amino acid sequences of the heavy chain variable (VH) region of SEQ ID NO: 216 and the light chain variable (VL) region of SEQ ID NO: 41, in Table 3a.

[0076] Also disclosed in Table 3a are other isolated antibodies or fragments reactive with TLR3 comprising both a heavy chain and a light chain variable region and wherein the antibody comprises the amino acid sequences of the heavy chain variable (VH) and the light chain variable (VL) regions.

Table 2b.

mAb	CDR definition	LCDR1		LCDR2		LCDR3	
		SEQ ID NO:	Sequence	SEQ ID NO:	Sequence	SEQ ID NO:	Sequence
14	IMGT	79	QSIGLY	80	AAS	85	QQAETVSPT
14	Kabat		RASQSIGLYLA		AASSLQS		QQAETVSPT
14	Chothia		SQSIGLY		AAS		AETVSP
14	Consensus	109	RASQSIGLYLA	110	AASSLQS	85	QQAETVSPT
15	IMGT	79	QSIGLY	80	AAS	87	QQGNTLSYT
15	Kabat		RASQSIGLYLA		AASSLQS		QQGNTLSYT
15	Chothia		SQSIGLY		AAS		GNTLSY
15	Consensus	109	RASQSIGLYLA	110	AASSLQS	113	QQGNTLSYT
15-1	IMGT	79	QSIGLY	80	AAS	87	QQGNTLSYT
15-1	Kabat		RASQSIGLYLA		AASSLQS		QQGNTLSYT
15-1	Chothia		SQSIGLY		AAS		GNTLSY
15-1	Consensus	109	RASQSIGLYLA	110	AASSLQS	113	QQGNTLSYT
15-2	IMGT	79	QSIGLY	80	AAS	87	QQGNTLSYT
15-2	Kabat		RASQSIGLYLA		AASSLQS		QQGNTLSYT
15-2	Chothia		SQSIGLY		AAS		GNTLSY
15-2	Consensus	109	RASQSIGLYLA	110	AASSLQS	113	QQGNTLSYT
15-3	IMGT	79	QSIGLY	80	AAS	87	QQGNTLSYT
15-3	Kabat		RASQSIGLYLA		AASSLQS		QQGNTLSYT
15-3	Chothia		SQSIGLY		AAS		GNTLSY
15-3	Consensus	109	RASQSIGLYLA	110	AASSLQS	113	QQGNTLSYT
15-4	IMGT	79	QSIGLY	80	AAS	87	QQGNTLSYT
15-4	Kabat		RASQSIGLYLA		AASSLQS		QQGNTLSYT
15-4	Chothia		SQSIGLY		AAS		GNTLSY
15-4	Consensus	109	RASQSIGLYLA	110	AASSLQS	113	QQGNTLSYT
15-5	IMGT	79	QSIGLY	80	AAS	87	QQGNTLSYT
15-5	Kabat		RASQSIGLYLA		AASSLQS		QQGNTLSYT
15-5	Chothia		SQSIGLY		AAS		GNTLSY
15-5	Consensus	109	RASQSIGLYLA	110	AASSLQS	113	QQGNTLSYT

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(continued)

mAb	CDR definition	LCDR1		LCDR2		LCDR3	
		SEQ ID NO:	Sequence	SEQ ID NO:	Sequence	SEQ ID NO:	Sequence
15-6	IMGT	79	QSIGLY	80	AAS	87	QQGNTLSYT
15-6	Kabat		RASQSIGLYLA		AASSLQS		QQGNTLSYT
15-6	Chothia		SQSIGLY		AAS		GNTLSY
15-6	Consensus	109	RASQSIGLYLA	110	AASSLQS	113	QQGNTLSYT
15-7	IMGT		QSISSY	80	AAS	87	QQGNTLSYT
15-7	Kabat		RASQSISSYLA		AASSLQS		QQGNTLSYT
15-7	Chothia		SQSISSY		AAS		GNTLSY
15-7	Consensus	120	RASQSISSYLA	110	AASSLQS	113	QQGNTLSYT
15-8	IMGT	79	QSIGLY	80	AAS	87	QQGNTLSYT
15-8	Kabat		RASQSIGLYLN		AASSLQS		QQGNTLSYT
15-8	Chothia		SQSIGLY		AAS		GNTLSY
15-8	Consensus	121	RASQSIGLYLN	110	AASSLQS	113	QQGNTLSYT
15-9	IMGT	79	QSIGLY	80	AAS	87	QQGNTLSYT
15-9	Kabat		RASQSIGLYLA		AASSLQS		QQGNTLSYT
15-9	Chothia		SQSIGLY		AAS		GNTLSY
15-9	Consensus	109	RASQSIGLYLA	110	AASSLQS	113	QQGNTLSYT

Table 3a.

mAb	SEQ ID NO:			mAb	SEQ ID NO:	
	VH	VL			VH	VL
16	6	5		15-1	124	41
17	8	7		15-2	125	41
18	10	9		15-3	126	41
19	12	11		15-4	127	41
1	14	13		15-5	128	41
2	16	15		15-6	129	41
3	18	17		15-7	42	122
4	20	19		15-8	42	123
5	22	21		15-9	159	41
6	24	23		F17	198	197
7	26	25		F18	200	199
8	28	27		F19	202	201
9	30	29		c1811	164	163
10	32	31		9QVQ/QSV	212	209
11	34	33		10QVQ/QSV	213	210
12	36	35		12QVQ/QSV	214	211

(continued)

mAb	SEQ ID NO:		mAb	SEQ ID NO:	
	VH	VL		VH	VL
13	38	37	14EVQ	215	39
14	40	39	15EVQ	216	41
15	42	41			

[0077] Although the embodiments illustrated in the Examples comprise pairs of variable regions, one from a heavy and one from a light chain, a skilled artisan will recognize that alternative instances may comprise single heavy or light chain variable regions. The single variable region can be used to screen for variable domains capable of forming a two-domain specific antigen-binding fragment capable of, for example, binding to TLR3. The screening may be accomplished by phage display screening methods using for example hierarchical dual combinatorial approach disclosed in PCT Publ. No. WO92/01047. In this approach, an individual colony containing either a H or L chain clone is used to infect a complete library of clones encoding the other chain (L or H), and the resulting two-chain specific antigen-binding domain is selected in accordance with phage display techniques as described.

[0078] In other embodiments, the invention provides an isolated antibody or fragment reactive with TLR3 according to claim 1 comprising both a heavy chain and a light chain variable regions having amino acid sequences at least 95% identical to the variable region amino acid sequence as shown in Table 3a.

[0079] In another aspect, the invention provides an isolated antibody or fragment comprising the heavy chain of SEQ ID NO: 220 and SEQ ID NO: 156.

[0080] In another aspect, the invention provides an isolated antibody according to claim 1 having certain heavy chain and light chain amino acid sequences as shown in Table 3b.

[0081] Also disclosed herein are isolated polynucleotides encoding any of the antibodies of the invention or their complement. Certain exemplary polynucleotides are disclosed herein, however, other polynucleotides which, given the degeneracy of the genetic code or codon preferences in a given expression system, encode the antibody antagonists of the invention are also disclosed.

[0082] Exemplary antibody antagonists may be antibodies of the IgG, IgD, IgG, IgA or IgM isotypes. Additionally, such antibody antagonists can be post-translationally modified by processes such as glycosylation, isomerization, deglycosylation or non-naturally occurring covalent modification such as the addition of polyethylene glycol (PEG) moieties (pegylation) and lipidation. Such modifications may occur *in vivo* or *in vitro*. For example, the antibodies of the invention can be conjugated to polyethylene glycol (PEGylated) to improve their pharmacokinetic profiles. Conjugation can be carried out by techniques known to those skilled in the art. Conjugation of therapeutic antibodies with PEG has been shown to enhance pharmacodynamics while not interfering with function. See Deckert et al., Int. J. Cancer 87:382-390, 2000; Knight et al., Platelets 15:409-418, 2004; Leong et al., Cytokine 16:106-119, 2001; and Yang et al., Protein Eng. 16:761-770, 2003.

Table 3b.

mAb	Heavy chain	Light chain
	SEQ ID NO:	SEQ ID NO:
14	102	155
15	102	156
15-1	130	156
15-2	131	156
15-3	132	156
15-4	133	156
15-5	134	156
15-6	135	156
15-7	102	157

(continued)

mAb	Heavy chain	Light chain
	SEQ ID NO:	SEQ ID NO:
15-8	102	158
15-9	160	156
F17	204	203
F18	206	205
F19	208	207
14EVQ	220	155
15EVQ	220	156
5429	166	165
c1811	168	167

[0083] Pharmacokinetic properties of the antibodies of the invention could also be enhanced through Fc modifications by techniques known to those skilled in the art. For example, IgG4 isotype heavy chains contain a Cys-Pro-Ser-Cys (CPSC) motif in the hinge region capable of forming either inter- or intra-heavy chain disulfide bonds, *i.e.*, the two Cys residues in the CPSC motif may disulfide bond with the corresponding Cys residues in the other heavy chain (inter) or the two Cys residues within a given CPSC motif may disulfide bond with each other (intra). It is believed that *in vivo* isomerase enzymes are capable of converting inter-heavy chain bonds of IgG4 molecules to intra-heavy chain bonds and *vice versa* (Aalberse and Schuurman, Immunology 105:9-19, 2002). Accordingly, since the heavy:light chain (H:L) pairs in those IgG4 molecules with intra-heavy chain bonds in the hinge region are not covalently associated with each other, they may dissociate into H:L monomers that then reassociate with H:L monomers derived from other IgG4 molecules forming bispecific, heterodimeric IgG4 molecules. In a bispecific IgG antibody the two Fabs of the antibody molecule differ in the epitopes that they bind. Substituting the Ser residue in the hinge region CPSC motif of IgG4 with Pro results in "IgG1-like behavior," *i.e.*, the molecules form stable disulfide bonds between heavy chains and therefore, are not susceptible to H:L exchange with other IgG4 molecules. In one embodiment, the antibodies of the invention will comprise an IgG4 Fc domain with a S to P mutation in the CPSC motif. The location of the CPSC motif is typically found at residue 228 of a mature heavy chain but can change depending on CDR lengths.

[0084] Further, sites can be removed that affect binding to Fc receptors other than an FcRn salvage receptor in the antibodies of the invention. For example, the Fc receptor binding regions involved in ADCC activity can be removed in the antibodies of the invention. For example, mutation of Leu234/Leu235 in the hinge region of IgG1 to L234A/L235A or Phe235/Leu236 in the hinge region of IgG4 to P235A/L236A minimizes FcR binding and reduces the ability of the immunoglobulin to mediate complement dependent cytotoxicity and ADCC. In one embodiment, the antibodies of the invention will comprise an IgG4 Fc domain with P235A/L236A mutations. The location of these residues identified above is typical in a mature heavy chain but can change depending on CDR lengths. Exemplary antibodies having P235A/L236A mutations are antibodies having heavy chains encoded by sequence shown in SEQ ID NOs: 218, 219 or 220.

[0085] Fully human, human-adapted, humanized and affinity-matured antibody molecules or antibody fragments are within the scope of the invention as are fusion proteins and chimeric proteins. Antibody affinity towards an antigen may be improved by rational design or random affinity maturation using well-known methods such as random or directed mutagenesis, or employing phage display libraries. For example, variation of Vernier Zone residues that mostly reside in the framework region can be employed to modulate affinity of an antibody as described in US Pat. No. 6,639,055. Recently, Almagro et al. defined "Affinity Determining Residues", ADRs, that reside in the CDRs, and whose engineering can increase affinity (Cobaugh et al., J Mol Biol. 378: 622-633, 2008).

[0086] Fully human, human-adapted, humanized, affinity-matured antibody molecules or antibody fragments modified to improve stability, selectivity, cross-reactivity, affinity, immunogenicity or other desirable biological or biophysical property are within the scope of the invention. Stability of an antibody is influenced by a number of factors, including (1) core packing of individual domains that affects their intrinsic stability, (2) protein/protein interface interactions that have impact upon the HC and LC pairing, (3) burial of polar and charged residues, (4) H-bonding network for polar and charged residues; and (5) surface charge and polar residue distribution among other intra- and intermolecular forces (Worn et al., J. Mol. Biol., 305:989-1010, 2001). Potential structure destabilizing residues may be identified based upon the crystal structure of the antibody or by molecular modeling in certain cases, and the effect of the residues on antibody stability can be tested by generating and evaluating variants harboring mutations in the identified residues. One of the ways to

increase antibody stability is to raise the thermal transition midpoint (T_m) as measured by differential scanning calorimetry (DSC). In general, the protein T_m is correlated with its stability and inversely correlated with its susceptibility to unfolding and denaturation in solution and the degradation processes that depend on the tendency of the protein to unfold (Remmele et al., Biopharm., 13:36-46, 2000). A number of studies have found correlation between the ranking of the physical stability of formulations measured as thermal stability by DSC and physical stability measured by other methods (Gupta et al., AAPS PharmSci. 5E8, 2003; Zhang et al., J. Pharm. Sci. 93:3076-3089, 2004; Maa et al., Int. J. Pharm., 140:155-168, 1996; Bedu-Addo et al., Pharm. Res., 21:1353-1361, 2004; Remmele et al., Pharm. Res., 15:200-208, 1997). Formulation studies suggest that a Fab T_m has implication for long-term physical stability of a corresponding mAb. Differences in amino acids in either framework or within the CDRs could have significant effects on the thermal stability of the Fab domain (Yasui, et al., FEBS Lett. 353:143-146, 1994).

[0087] The antibody antagonists of the invention may bind TLR3 with a K_d less than or equal to about 10^{-7} , 10^{-8} , 10^{-9} , 10^{-10} , 10^{-11} or 10^{-12} M. The affinity of a given molecule for TLR3, such as an antibody can be determined experimentally using any suitable method. Such methods may utilize Biacore or KinExA instrumentation, ELISA or competitive binding assays known to those skilled in the art.

[0088] Antibody antagonists binding a given TLR3 homolog with a desired affinity can be selected from libraries of variants or fragments by techniques including antibody affinity maturation. Antibody antagonists can be identified based on their inhibition of TLR3 biological activity using any suitable method. Such methods may utilize reporter-gene assays or assays measuring cytokine production using well known methods and as described in the application.

[0089] Another embodiment of the invention is a vector comprising at least one polynucleotide of the invention. Such vectors may be plasmid vectors, viral vectors, vectors for baculovirus expression, transposon based vectors or any other vector suitable for introduction of the polynucleotides of the invention into a given organism or genetic background by any means.

[0090] Also disclosed herein is a host cell comprising polynucleotides such as a polynucleotide encoding a polypeptide comprising an immunoglobulin heavy chain variable region having the amino acid sequence shown in SEQ ID NO: 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 124, 125, 126, 127, 128, 129, 159, 198, 200, 202, 164, 212, 213, 214, 215 or 216 or an immunoglobulin light chain variable region having the amino acid sequence shown in SEQ ID NO: 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 122, 123, 197, 199, 201, 163, 209 or 210.

[0091] Also disclosed herein is a host cell comprising a polynucleotide encoding a polypeptide comprising an immunoglobulin heavy chain having the amino acid sequence shown in SEQ ID NO: 102, 130, 131, 132, 133, 134, 135, 160, 204, 206, 208, 220, 166 or 168, or an immunoglobulin light chain having the amino acid sequence shown in SEQ ID NO: 155, 156, 157, 158, 203, 205, 207, 165 or 167. Such host cells may be eukaryotic cells, bacterial cells, plant cells or archeal cells. Exemplary eukaryotic cells may be of mammalian, insect, avian or other animal origins. Mammalian eukaryotic cells include immortalized cell lines such as hybridomas or myeloma cell lines such as SP2/0 (American Type Culture Collection (ATCC), Manassas, VA, CRL-1581), NS0 (European Collection of Cell Cultures (ECACC), Salisbury, Wiltshire, UK, ECACC No. 85110503), FO (ATCC CRL-1646) and Ag653 (ATCC CRL-1580) murine cell lines. An exemplary human myeloma cell line is U266 (ATCC CRL-TIB-196). Other useful cell lines include those derived from Chinese Hamster Ovary (CHO) cells such as CHO-K1SV (Lonza Biologics, Walkersville, MD), CHO-K1 (ATCC CRL-61) or DG44.

[0092] Also disclosed herein is a method of making an antibody reactive with TLR3 comprising culturing a host cell of the disclosure and recovering the antibody produced by the host cell. Methods of making antibodies and purifying them are well known in the art.

[0093] Also disclosed herein is a hybridoma cell line that produces an antibody of the invention.

[0094] Also disclosed herein is an isolated antibody or fragment thereof that is reactive with TLR3, wherein the antibody binds at least one TLR3 amino acid residue selected from a group consisting of (a) residues K467, R488, or R489 of SEQ ID NO: 2; (b) residue K467 of SEQ ID NO: 2; (c) residue R489 of SEQ ID NO: 2; (d) residues K467 and R489 of SEQ ID NO: 2; and (e) residues K467, R488, and R489 of SEQ ID NO: 2. The isolated antibody may further bind at least one TLR3 amino acid residue selected from the residues Y465, Y468, N517, D536, Q538, H539, N541, E570 or K619 of SEQ ID NO:2.

[0095] Also disclosed herein is an isolated antibody or fragment thereof, wherein the antibody binds at least on TLR3 amino acid residue selected from a group consisting of residues D116 or K145 of SEQ ID NO: 2.

[0096] Several well known methodologies can be employed to determine the binding epitope of the antibodies of the invention. For example, when the structures of both individual components are known, *in silico* protein-protein docking can be carried out to identify compatible sites of interaction. Hydrogen-deuterium (H/D) exchange can be carried out with the antigen and antibody complex to map regions on the antigen that may be bound by the antibody. Segment and point mutagenesis of the antigen can be used to locate amino acids important for antibody binding. For large proteins such as TLR3, point mutagenesis mapping is simplified when the binding site is first localized to a region on the protein, such as by docking, segment mutagenesis or H/D exchange.

[0097] Also disclosed herein is an isolated antibody or fragment thereof reactive with TLR3 that competes for TLR3

binding with a monoclonal antibody, wherein the monoclonal antibody comprises the amino acid sequences of heavy chain complementarity determining regions (CDRs) 1, 2 and 3, as shown in SEQ ID NO:s 82, 86 and 84 and the amino acid sequences of light chain CDRs 1, 2 and 3, as shown in SEQ ID NO:s 79, 80 and 87; or the amino acid sequence of heavy chain variable regions (VH) as shown in SEQ ID NO: 216 and the amino acid sequence of light chain variable regions (VL) as shown in SEQ ID NO: 41. Exemplary monoclonal antibodies of the invention are an isolated antibody comprising a heavy chain variable region having an amino acid sequence shown in SEQ ID NO: 216 and a light chain variable region amino acid sequence shown in SEQ ID NO: 41, and an antibody comprising a heavy chain variable region having an amino acid sequence shown in SEQ ID NO: 214 and a light chain variable region amino acid sequence shown in SEQ ID NO: 211.

[0098] Competition between binding to TLR3 can be assayed *in vitro* using well known methods. For example, binding of MSD Sulfo-Tag™ NHS-ester -labeled antibody to TLR3 in the presence of an unlabeled antibody can be assessed by ELISA. An exemplary antibody of the invention is mAb 15. Other exemplary antibodies of the disclosure are mAb 12 and mAb c1811 (see Table 3a). Previously described anti-TLR3 antibodies c1068 and its derivatives (described in PCT Publ. No. WO06/060513A2), TLR3.7 (eBiosciences, cat no 14-9039) and Imgenex IMG-315A (Imgenex IMG-315A; generated against human TLR3 amino acids 55-70, VLNLTHNQLRRLPAAN) do not compete with binding to TLR3 with mAbs 12, 15 or c1811 as shown in Example 5.

[0099] Another aspect of the invention is an isolated antibody reactive with TLR3 comprising the sequences recited in the claims, wherein the antibody has at least one of the following properties:

- a. reduces human TLR3 biological activity in an *in vitro* poly(I:C) NF-κB reporter gene assay >50% at <1 μg/ml;
- b. inhibits >60% of IL-6 or CXCL5/IP-10 production from BEAS-2B cells stimulated with <100 ng/ml poly(I:C) at <10 μg/ml;
- c. inhibits >50% of IL-6 or CXCL5/IP-10 production from BEAS-2B cells stimulated with <100 ng/ml poly(I:C) at <0.4 μg/ml;
- d. inhibits >50% of IL-6 production from NHBE cells stimulated with 62.5 ng/ml poly(I:C) at <5 μg/ml;
- e. inhibits >50% of IL-6 production from NHBE cells stimulated with 62.5 ng/ml poly(I:C) at <1 μg/ml;
- f. inhibits >20% of poly(I:C)-induced IFN-γ, IL-6 or IL-12 production by PBMC cells at <1 μg/ml.
- g. inhibits cynomolgus TLR3 biological activity in an *in vitro* NF-κB reporter gene assay with IC50 <10 μg/ml; or
- h. inhibits cynomolgus TLR3 biological activity in an *in vitro* ISRE reporter gene assay with IC50 <5 μg/ml.

Methods of Treatment

[0100] TLR3 antagonists of the invention, for example TLR3 antibody antagonists, can be used to modulate the immune system. While not wishing to be bound by any particular theory, the antagonists of the invention may modulate the immune system by preventing or reducing ligand binding to TLR3, dimerization of TLR3, TLR3 internalization or TLR3 trafficking. An isolated antibody or fragment thereof of the invention may be used to treat an animal patient belonging to any classification. Examples of such animals include mammals such as humans, rodents, dogs, cats and farm animals. For example, the antibodies of the invention are useful in antagonizing TLR3 activity, in the treatment of inflammation, inflammatory and metabolic diseases and are also useful in the preparation of a medicament for such treatment wherein the medicament is prepared for administration in dosages defined herein.

[0101] Generally, inflammatory conditions, infection-associated conditions or immune-mediated inflammatory disorders that may be prevented or treated by administration of the TLR3 antibody antagonists of the invention include those mediated by cytokines or chemokines and those conditions which result wholly or partially from activation of TLR3 or signaling through the TLR3 pathway. Examples of such inflammatory conditions include sepsis-associated conditions, inflammatory bowel diseases, autoimmune disorders, inflammatory disorders and infection-associated conditions. It is also thought that cancers, cardiovascular and metabolic conditions, neurologic and fibrotic conditions can be prevented or treated by administration of the TLR3 antibody antagonists of the invention. Inflammation may affect a tissue or be systemic. Exemplary affected tissues are the respiratory tract, lung, the gastrointestinal tract, small intestine, large intestine, colon, rectum, the cardiovascular system, cardiac tissue, blood vessels, joint, bone and synovial tissue, cartilage, epithelium, endothelium, hepatic or adipose tissue. Exemplary systemic inflammatory conditions are cytokine storm or hypercytokinemia, systemic inflammatory response syndrome (SIRS), graft versus host disease (GVHD), acute respiratory distress syndrome (ARDS), severe acute respiratory distress syndrome (SARS), catastrophic anti-phospholipid syndrome, severe viral infections, influenza, pneumonia, shock, or sepsis.

[0102] Inflammation is a protective response by an organism to fend off an invading agent. Inflammation is a cascading event that involves many cellular and humoral mediators. On one hand, suppression of inflammatory responses can leave a host immunocompromised; however, if left unchecked, inflammation can lead to serious complications including chronic inflammatory diseases (e.g. asthma, psoriasis, arthritis, rheumatoid arthritis, multiple sclerosis, inflammatory bowel disease and the like), septic shock and multiple organ failure. Importantly, these diverse disease states share

common inflammatory mediators, such as cytokines, chemokines, inflammatory cells and other mediators secreted by these cells.

[0103] TLR3 activation by its ligands poly(I:C), dsRNA or endogenous mRNA leads to activation of signaling pathways resulting in synthesis and secretion of pro-inflammatory cytokines, activation and recruitment of inflammatory cells, such as macrophages, granulocytes, neutrophils and eosinophils, cell death, and tissue destruction. TLR3 induces secretion of IL-6, IL-8, IL-12, TNF- α , MIP-1, CXCL5/IP-10 and RANTES, and other pro-inflammatory cytokines and chemokines implicated in immune cell recruitment and activation, thus contributing to tissue destruction in autoimmune and other inflammatory diseases. TLR3 ligand endogenous mRNA is released from necrotic cells during inflammation, and may result in a positive feedback loop to activate TLR3 and perpetuate inflammation and further tissue damage. TLR3 antagonists, such as TLR3 antibody antagonists, may normalize cytokine secretion, reduce recruitment of inflammatory cells, and reduce tissue damage and cell death. Therefore, TLR3 antagonists have therapeutic potential to treat inflammation and a spectrum of inflammatory conditions.

[0104] One example of an inflammatory condition is sepsis-associated condition that may include systemic inflammatory response syndrome (SIRS), septic shock or multiple organ dysfunction syndrome (MODS). dsRNA released by viral, bacterial, fungal, or parasitic infection and by necrotic cells can contribute to the onset of sepsis. While not wishing to be bound by an particular theory, it is believed that treatment with TLR3 antagonists can provide a therapeutic benefit by extending survival times in patients suffering from sepsis-associated inflammatory conditions or prevent a local inflammatory event (e.g., in the lung) from spreading to become a systemic condition, by potentiating innate antimicrobial activity, by demonstrating synergistic activity when combined with antimicrobial agents, by minimizing the local inflammatory state contributing to the pathology, or any combination of the foregoing. Such intervention may be sufficient to permit additional treatment (e.g., treatment of underlying infection or reduction of cytokine levels) necessary to ensure patient survival. Sepsis can be modeled in animals, such as mice, by the administration of D-galactosamine and poly(I:C). In such models, D-galactosamine is a hepatotoxin which functions as a sepsis sensitizer and poly(I:C) is a sepsis-inducing molecule that mimics dsRNA and activates TLR3. TLR3 antagonist treatment may increase animal survival rates in a murine model of sepsis, and thus TLR3 antagonists may be useful in the treatment of sepsis.

[0105] Gastrointestinal inflammation is inflammation of a mucosal layer of the gastrointestinal tract, and encompasses acute and chronic inflammatory conditions. Acute inflammation is generally characterized by a short time of onset and infiltration or influx of neutrophils. Chronic inflammation is generally characterized by a relatively longer period of onset and infiltration or influx of mononuclear cells. Mucosal layer may be mucosa of the bowel (including the small intestine and large intestine), rectum, stomach (gastric) lining, or oral cavity. Exemplary chronic gastrointestinal inflammatory conditions are inflammatory bowel disease (IBD), colitis induced by environmental insults (e.g., gastrointestinal inflammation (e.g., colitis) caused by or associated with (e.g., as a side effect) a therapeutic regimen, such as administration of chemotherapy, radiation therapy, and the like), infections colitis, ischemic colitis, collagenous or lymphocytic colitis, necrotizing enterocolitis, colitis in conditions such as chronic granulomatous disease or celiac disease, food allergies, gastritis, infectious gastritis or enterocolitis (e.g., *Helicobacter pylori*-infected chronic active gastritis) and other forms of gastrointestinal inflammation caused by an infectious agent.

[0106] Inflammatory bowel disease (IBD) includes a group of chronic inflammatory disorders of generally unknown etiology, e.g., ulcerative colitis (UC) and Crohn's disease (CD). Clinical and experimental evidence suggest that the pathogenesis of IBD is multifactorial involving susceptibility genes and environmental factors. In inflammatory bowel disease, the tissue damage results from an inappropriate or exaggerated immune response to antigens of the gut microflora. Several animal models for inflammatory bowel diseases exist. Some of the most widely used models are the 2,4,6-trinitrobenesulfonic acid/ethanol (TNBS)-induced colitis model or the oxazalone model, which induce chronic inflammation and ulceration in the colon (Neurath et al., *Intern. Rev. Immunol* 19:51-62, 2000). Another model uses dextran sulfate sodium (DSS), which induces an acute colitis manifested by bloody diarrhea, weight loss, shortening of the colon and mucosal ulceration with neutrophil infiltration. DSS-induced colitis is characterized histologically by infiltration of inflammatory cells into the lamina propria, with lymphoid hyperplasia, focal crypt damage, and epithelial ulceration (Hendrickson et al., *Clinical Microbiology Reviews* 15:79-94, 2002). Another model involves the adoptive transfer of naive CD45RB^{high} CD4 T cells to RAG or SCID mice. In this model, donor naive T cells attack the recipient gut causing chronic bowel inflammation and symptoms similar to human inflammatory bowel diseases (Read and Powrie, *Curr. Protoc. Immunol.* Chapter 15 unit 15.13, 2001). The administration of antagonists of the present invention in any of these models can be used to evaluate the potential efficacy of those antagonists to ameliorate symptoms and alter the course of diseases associated with inflammation in the gut, such as inflammatory bowel disease. Several treatment options for IBD are available, for example anti-TNF- α antibody therapies have been used for a decade to treat Crohn's disease (Van Assche et al., *Eur. J. Pharmacol.* Epub Oct 2009). However, a significant percentage of patients are refractory to the current treatments (Hanauer et al., *Lancet* 359:1541-1549, 2002; Hanauer et al., *Gastroenterology* 130:323-333, 2006), and thus new therapies targeting refractory patient populations are needed.

[0107] Another example of an inflammatory condition is an inflammatory pulmonary condition. Exemplary inflammatory pulmonary conditions include infection-induced pulmonary conditions including those associated with viral, bacterial,

fungal, parasite or prion infections; allergen-induced pulmonary conditions; pollutant-induced pulmonary conditions such as asbestosis, silicosis, or berylliosis; gastric aspiration-induced pulmonary conditions, immune dysregulation, inflammatory conditions with genetic predisposition such as as cystic fibrosis, and physical trauma-induced pulmonary conditions, such as ventilator injury. These inflammatory conditions also include asthma, emphysema, bronchitis, chronic obstructive pulmonary disease (COPD), sarcoidosis, histiocytosis, lymphangiomyomatosis, acute lung injury, acute respiratory distress syndrome, chronic lung disease, bronchopulmonary dysplasia, community-acquired pneumonia, nosocomial pneumonia, ventilator - associated pneumonia, sepsis, viral pneumonia, influenza infection, parainfluenza infection, rotavirus infection, human metapneumovirus infection, respiratory syncytial virus infection and aspergillus or other fungal infections. Exemplary infection-associated inflammatory diseases may include viral or bacterial pneumonia, including severe pneumonia, cystic fibrosis, bronchitis, airway exacerbations and acute respiratory distress syndrome (ARDS). Such infection-associated conditions may involve multiple infections such as a primary viral infection and a secondary bacterial infection.

[0108] Asthma is an inflammatory disease of the lung that is characterized by airway hyperresponsiveness ("AHR"), bronchoconstriction, wheezing, eosinophilic or neutrophilic inflammation, mucus hypersecretion, subepithelial fibrosis, and elevated IgE levels. Patients with asthma experience "exacerbations", a worsening of symptoms, most commonly due to microbial infections of the respiratory tract (e.g. rhinovirus, influenza virus, Haemophilus influenza, etc.). Asthmatic attacks can be triggered by environmental factors (e.g. ascarids, insects, animals (e.g., cats, dogs, rabbits, mice, rats, hamsters, guinea pigs and birds), fungi, air pollutants (e.g., tobacco smoke), irritant gases, fumes, vapors, aerosols, chemicals, pollen, exercise, or cold air. Apart from asthma, several chronic inflammatory diseases affecting the lung are characterized by neutrophil infiltration to the airways, for example chronic obstructive pulmonary disease (COPD), bacterial pneumonia and cystic fibrosis (Linden et al., Eur. Respir. J. 15:973-977, 2000; Rahman et al., Clin. Immunol. 115:268-276, 2005), and diseases such as COPD, allergic rhinitis, and cystic fibrosis are characterized by airway hyperresponsiveness (Fahy and O'Byrne, Am. J. Respir. Crit. Care Med. 163:822-823, 2001). Commonly used animal models for asthma and airway inflammation include the ovalbumin challenge model and methacholine sensitization models (Hessel et al., Eur. J. Pharmacol. 293:401-412, 1995). Inhibition of cytokine and chemokine production from cultured human bronchial epithelial cells, bronchial fibroblasts or airway smooth muscle cells can also be used as *in vitro* models. The administration of antagonists of the present invention to any of these models can be used to evaluate the use of those antagonists to ameliorate symptoms and alter the course of asthma, airway inflammation, COPD and the like.

[0109] Other inflammatory conditions and neuropathies, which may be prevented or treated by the isolated antibody or fragment thereof of the invention are those caused by autoimmune diseases. These conditions and neuropathies include multiple sclerosis, systemic lupus erythematosus, and neurodegenerative and central nervous system (CNS) disorders including Alzheimer's disease, Parkinson's disease, Huntington's disease, bipolar disorder and Amyotrophic Lateral Sclerosis (ALS), liver diseases including primary biliary cirrhosis, primary sclerosing cholangitis, non-alcoholic fatty liver disease/steatohepatitis, fibrosis, hepatitis C virus (HCV) and hepatitis B virus (HBV), diabetes and insulin resistance, cardiovascular disorders including atherosclerosis, cerebral hemorrhage, stroke and myocardial infarction, arthritis, rheumatoid arthritis, psoriatic arthritis and juvenile rheumatoid arthritis (JRA), osteoporosis, osteoarthritis, pancreatitis, fibrosis, encephalitis, psoriasis, Giant cell arteritis, ankylosing spondylitis, autoimmune hepatitis, human immunodeficiency virus (HIV), inflammatory skin conditions, transplant, cancer, allergies, endocrine diseases, wound repair, other autoimmune disorders, airway hyperresponsiveness and cell, virus, or prion-mediated infections or disorders.

[0110] Arthritis, including osteoarthritis, rheumatoid arthritis, arthritic joints as a result of injury, and the like, are common inflammatory conditions which would benefit from the therapeutic use of anti-inflammatory proteins, such as the antagonists of the present invention. For example, rheumatoid arthritis (RA) is a systemic disease that affects the entire body and is one of the most common forms of arthritis. Since rheumatoid arthritis results in tissue damage, TLR3 ligands could be present at the site of the inflammation. Activation of TLR3 signaling may perpetuate inflammation and further tissue damage in the inflamed joint. Several animal models for rheumatoid arthritis are known in the art. For example, in the collagen-induced arthritis (CIA) model, mice develop chronic inflammatory arthritis that closely resembles human rheumatoid arthritis. Administration of the TLR3 antagonists of the present invention to the CIA model mice can be used to evaluate the use of these antagonists to ameliorate symptoms and alter the course of diseases.

[0111] Diabetes mellitus, diabetes, refers to a disease process derived from multiple causative factors and characterized by hyperglycemia (LeRoith et al., (eds.), Diabetes Mellitus, Lippincott-Raven Publishers, Philadelphia, Pa. U.S.A. 1996), and all references cited therein. Uncontrolled hyperglycemia is associated with increased and premature mortality due to an increased risk for microvascular and macrovascular diseases, including nephropathy, neuropathy, retinopathy, hypertension, cerebrovascular disease and coronary heart disease. Therefore, control of glucose homeostasis is a critically important approach for the treatment of diabetes.

[0112] Underlying defects lead to a classification of diabetes into two major groups: type I diabetes (insulin dependent diabetes mellitus, IDDM), which arises when patients lack insulin-producing beta-cells in their pancreatic glands, and

type 2 diabetes (non-insulin dependent diabetes mellitus, NIDDM), which occurs in patients with an impaired beta-cell insulin secretion and/or resistance to insulin action.

[0113] Type 2 diabetes is characterized by insulin resistance accompanied by relative, rather than absolute, insulin deficiency. In insulin resistant individuals, the body secretes abnormally high amounts of insulin to compensate for this defect. When inadequate amounts of insulin are present to compensate for insulin resistance and adequately control glucose, a state of impaired glucose tolerance develops. In a significant number of individuals, insulin secretion declines further and the plasma glucose level rises, resulting in the clinical state of diabetes. Adiposity-associated inflammation has been strongly implicated in the development of insulin resistance, type 2 diabetes, dyslipidemia and cardiovascular disease. Obese adipose recruits and retains macrophages and can produce excessive pro-inflammatory cytokines including TNF- α and IL-6, free fatty acids and adipokines, which can interfere with insulin signaling and induce insulin resistance. TLR3 activation on macrophages may contribute to the pro-inflammatory status of the adipose. Several animal models of insulin resistance are known. For example, in a diet-induced obesity model (DIO) animals develop hyperglycemia and insulin resistance accompanied by weight gain. Administration of TLR3 antagonists of the present invention to the DIO model can be used to evaluate the use of the antagonists to ameliorate complications associated with type 2 diabetes and alter the course of the disease.

[0114] Exemplary cancers may include at least one malignant disease in a cell, tissue, organ, animal or patient, including, but not limited to leukemia, acute leukemia, acute lymphoblastic leukemia (ALL), B-cell or T-cell ALL, acute myeloid leukemia (AML), chronic myelocytic leukemia (CML), chronic lymphocytic leukemia (CLL), hairy cell leukemia, myelodysplastic syndrome (MDS), a lymphoma, Hodgkin's disease, a malignant lymphoma, non-Hodgkin's lymphoma, Burkitt's lymphoma, multiple myeloma, Kaposi's sarcoma, colorectal carcinoma, pancreatic carcinoma, renal cell carcinoma, breast cancer, nasopharyngeal carcinoma, malignant histiocytosis, paraneoplastic syndrome/hypercalcemia of malignancy, solid tumors, adenocarcinomas, squamous cell carcinomas, sarcomas, malignant melanoma, particularly metastatic melanoma, hemangioma, metastatic disease, cancer related bone resorption and cancer related bone pain.

[0115] Exemplary cardiovascular diseases may include cardiovascular disease in a cell, tissue, organ, animal, or patient, including, but not limited to, cardiac stun syndrome, myocardial infarction, congestive heart failure, stroke, ischemic stroke, hemorrhage, arteriosclerosis, atherosclerosis, restenosis, diabetic atherosclerotic disease, hypertension, arterial hypertension, renovascular hypertension, syncope, shock, syphilis of the cardiovascular system, heart failure, cor pulmonale, primary pulmonary hypertension, cardiac arrhythmias, atrial ectopic beats, atrial flutter, atrial fibrillation (sustained or paroxysmal), post perfusion syndrome, cardiopulmonary bypass inflammation response, chaotic or multifocal atrial tachycardia, regular narrow QRS tachycardia, specific arrhythmias, ventricular fibrillation, His bundle arrhythmias, atrioventricular block, bundle branch block, myocardial ischemic disorders, coronary artery disease, angina pectoris, myocardial infarction, cardiomyopathy, dilated congestive cardiomyopathy, restrictive cardiomyopathy, valvular heart diseases, endocarditis, pericardial disease, cardiac tumors, aortic and peripheral aneurysms, aortic dissection, inflammation of the aorta, occlusion of the abdominal aorta and its branches, peripheral vascular disorders, occlusive arterial disorders, peripheral atherosclerotic disease, thromboangitis obliterans, functional peripheral arterial disorders, Raynaud's phenomenon and disease, acrocyanosis, erythromelalgia, venous diseases, venous thrombosis, varicose veins, arteriovenous fistula, lymphedema, lipedema, unstable angina, reperfusion injury, post pump syndrome and ischemia-reperfusion injury.

[0116] Exemplary neurological diseases may include neurologic disease in a cell, tissue, organ, animal or patient, including, but not limited to neurodegenerative diseases, multiple sclerosis, migraine headache, AIDS dementia complex, demyelinating diseases, such as multiple sclerosis and acute transverse myelitis; extrapyramidal and cerebellar disorders such as lesions of the corticospinal system; disorders of the basal ganglia or cerebellar disorders; hyperkinetic movement disorders such as Huntington's Chorea and senile chorea; drug-induced movement disorders, such as those induced by drugs which block CNS dopamine receptors; hypokinetic movement disorders, such as Parkinson's disease; Progressive supranuclear Palsy; structural lesions of the cerebellum; spinocerebellar degenerations, such as spinal ataxia, Friedreich's ataxia, cerebellar cortical degenerations, multiple systems degenerations (Mencel, Dejerine-Thomas, Shy-Drager, and Machado-Joseph); systemic disorders (Refsum's disease, abetalipoproteinemia, ataxia, telangiectasia, and mitochondrial multisystem disorder); demyelinating core disorders, such as multiple sclerosis, acute transverse myelitis; and disorders of the motor unit such as neurogenic muscular atrophies (anterior horn cell degeneration, such as amyotrophic lateral sclerosis, infantile spinal muscular atrophy and juvenile spinal muscular atrophy); Alzheimer's disease; Down's Syndrome in middle age; Diffuse Lewy body disease; Senile Dementia of Lewy body type; Wernicke-Korsakoff syndrome; chronic alcoholism; Creutzfeldt-Jakob disease; Subacute sclerosing panencephalitis, Hallerorden-Spatz disease and Dementia pugilistica.

[0117] Exemplary fibrotic conditions may include liver fibrosis (including but not limited to alcohol-induced cirrhosis, viral-induced cirrhosis, autoimmune-induced hepatitis); lung fibrosis (including but not limited to scleroderma, idiopathic pulmonary fibrosis); kidney fibrosis (including but not limited to scleroderma, diabetic nephritis, glomerular nephritis, lupus nephritis); dermal fibrosis (including but not limited to scleroderma, hypertrophic and keloid scarring, burns); myelofibrosis; neurofibromatosis; fibroma; intestinal fibrosis; and fibrotic adhesions resulting from surgical procedures.

In such a method, the fibrosis can be organ specific fibrosis or systemic fibrosis. The organ specific fibrosis can be associated with at least one of lung fibrosis, liver fibrosis, kidney fibrosis, heart fibrosis, vascular fibrosis, skin fibrosis, eye fibrosis, bone marrow fibrosis or other fibrosis. The lung fibrosis can be associated with at least one of idiopathic pulmonary fibrosis, drug induced pulmonary fibrosis, asthma, sarcoidosis or chronic obstructive pulmonary disease. The liver fibrosis can be associated with at least one of cirrhosis, schistosomiasis or cholangitis. The cirrhosis can be selected from alcoholic cirrhosis, post-hepatitis C cirrhosis, primary biliary cirrhosis. The cholangitis is sclerosing cholangitis. The kidney fibrosis can be associated with diabetic nephropathy or lupus glomerulosclerosis. The heart fibrosis can be associated with myocardial infarction. The vascular fibrosis can be associated with postangioplasty arterial restenosis or atherosclerosis. The skin fibrosis can be associated with burn scarring, hypertrophic scarring, keloid, or nephrogenic fibrosing dermatopathy. The eye fibrosis can be associated with retro-orbital fibrosis, postcataract surgery or proliferative vitreoretinopathy. The bone marrow fibrosis can be associated with idiopathic myelofibrosis or drug induced myelofibrosis. The other fibrosis can be selected from Peyronie's disease, Dupuytren's contracture or dermatomyositis. The systemic fibrosis can be systemic sclerosis or graft versus host disease.

Administration/Pharmaceutical Compositions

[0118] The "therapeutically effective amount" of the agent effective in the treatment or prevention of conditions where suppression of TLR3 activity is desirable can be determined by standard research techniques. For example, the dosage of the agent that will be effective in the treatment or prevention of inflammatory condition such as asthma, Crohn's Disease, ulcerative colitis or rheumatoid arthritis can be determined by administering the agent to relevant animal models, such as the models described herein.

[0119] In addition, *in vitro* assays can optionally be employed to help identify optimal dosage ranges. Selection of a particular effective dose can be determined (e.g., via clinical trials) by those skilled in the art based upon the consideration of several factors. Such factors include the disease to be treated or prevented, the symptoms involved, the patient's body mass, the patient's immune status and other factors known by the skilled artisan. The precise dose to be employed in the formulation will also depend on the route of administration, and the severity of disease, and should be decided according to the judgment of the practitioner and each patient's circumstances. Effective doses can be extrapolated from dose-response curves derived from *in vitro* or animal model test systems.

[0120] In the therapeutic uses of the invention, the TLR3 antagonist may be administered singly or in combination with at least one other molecule. Such additional molecules may be other TLR3 antagonist molecules or molecules with a therapeutic benefit not mediated by TLR3 receptor signaling. Antibiotics, antivirals, palliatives and other compounds that reduce cytokine levels or activity are examples of such additional molecules.

[0121] The mode of administration for therapeutic use of the agent of the invention may be any suitable route that delivers the agent to the host. Pharmaceutical compositions of these agents are particularly useful for parenteral administration, e.g., intradermal, intramuscular, intraperitoneal, intravenous, subcutaneous or intranasal.

[0122] The agent of the invention may be prepared as pharmaceutical compositions containing an effective amount of the agent as an active ingredient in a pharmaceutically acceptable carrier. The term "carrier" refers to a diluent, adjuvant, excipient, or vehicle with which the active compound is administered. Such pharmaceutical vehicles can be liquids, such as water and oils, including those of petroleum, animal, vegetable or synthetic origin, such as peanut oil, soybean oil, mineral oil, sesame oil and the like. For example, 0.4% saline and 0.3% glycine can be used. These solutions are sterile and generally free of particulate matter. They may be sterilized by conventional, well-known sterilization techniques (e.g., filtration). The compositions may contain pharmaceutically acceptable auxiliary substances as required to approximate physiological conditions such as pH adjusting and buffering agents, stabilizing, thickening, lubricating and coloring agents, etc. The concentration of the agent of the invention in such pharmaceutical formulation can vary widely, i.e., from less than about 0.5%, usually at or at least about 1% to as much as 15 or 20% by weight and will be selected primarily based on required dose, fluid volumes, viscosities, etc., according to the particular mode of administration selected.

[0123] Thus, a pharmaceutical composition of the invention for intramuscular injection could be prepared to contain 1 ml sterile buffered water, and between about 1 ng to about 100 mg, e.g. about 50 ng to about 30 mg or more preferably, about 5 mg to about 25 mg, of a TLR3 antibody antagonist of the invention. Similarly, a pharmaceutical composition of the invention for intravenous infusion could be made up to contain about 250 ml of sterile Ringer's solution, and about 1 mg to about 30 mg and preferably 5 mg to about 25 mg of an antagonist of the invention. Actual methods for preparing parenterally administrable compositions are well known and are described in more detail in, for example, "Remington's Pharmaceutical Science", 15th ed., Mack Publishing Company, Easton, PA.

[0124] The antibody antagonists of the invention can be lyophilized for storage and reconstituted in a suitable carrier prior to use. This technique has been shown to be effective with conventional immunoglobulins and protein preparations and art-known lyophilization and reconstitution techniques can be employed.

[0125] The present invention will now be described with reference to the following specific, non-limiting examples.

Example 1**Identification and Derivation of Anti-huTLR3 Antagonist mAbs**

[0126] The MorphoSys Human Combinatorial Antibody Library (HuCAL®) Gold phage display library (Morphosys AG, Martinsried, Germany) was used as a source of human antibody fragments and was panned against a purified TLR3 antigen generated from the expression of amino acids 1-703 of human TLR3 (huTLR3) (SEQ ID NO: 4) with a C-terminal poly-histidine tag and purified by immobilized metal affinity chromatography. Amino acids 1-703 correspond to the predicted extracellular domain (ECD) of huTLR3. Fab fragments (Fabs) that bound specifically to huTLR3 ECD were selected by presenting the TLR3 protein in a variety of ways so that a diverse set of antibody fragments could be identified, sequenced and confirmed as unique. From different panning strategies, 62 candidates (different V-region sequences) were identified as unique hTLR3 ECD binders.

[0127] The 62 candidates identified as huTLR3 ECD binders were screened for neutralizing activity in a range of cell-based assays relevant to identifying anti-inflammatory activity. Using preliminary activity data (see Example 2 below), four candidates (Fabs 16-19) defining families 16-19 were selected from the 62 as parents for CDR maturation of heavy chain CDR2 (HCDR2) and light chain CDR3 (LCDR3). One of the parental candidates (candidate 19) exhibited an N-linked glycosylation site in HCDR2; a Ser to Ala (S to A) mutation was made in this candidate to delete the site. Following CDR maturation of the four parental candidates, a total of 15 progeny candidates (candidates 1-15) were identified for further characterization as described in Example 2 below. A listing of the light and heavy chain variable regions present in each of the 19 candidates is shown in Table 3 above. The candidates are herein referred to as mAbs 1-19 or Fabs 1-19, depending whether they were Fabs or cloned as full length antibody chains (Example 3). Due to expression vector design, the mature amino termini of the variable regions for all candidates were QVE for heavy chain and DI for the light chain. The preferred sequences at these termini are those in the respective germline genes with high identity to the candidate sequences. For families 17 and 18 the germline sequences are QVQ for VH and SY for VL. For family 19, the sequences are EVQ for VH and DI for VL. The SY sequence is unique to the lambda subgroup 3 and there are reports of heterogeneity with either S or Y as the amino terminal residue. Thus, the QSV consensus terminus from the prominent lambda subgroup 1 was considered a more suitable replacement for DIE for VL of families 17 and 18. These changes were introduced into candidates 9, 10 and 12 from family 18 and candidates 14 and 15 from family 19. In this process, both the VH and VL regions of these antibodies were codon optimized. The amino acid sequences of the light chain variable region N-terminal germline variants of candidates 9, 10 and 11 are shown in SEQ ID NO:s 209-211, and the amino acid sequences of the heavy chain variable region N-terminal germline variants for candidates 9, 10, 12, 14, and 15 are shown in SEQ ID NO:s 212-216, respectively. The N-terminal variants of the candidates are herein referred to as candidate/mAb/Fab 9QVQ/QSV, 10QVQ/QSV, 12QVQ/QSV, 14EVQ or 15EVQ. The N-terminal germline variants were expressed as mAbs and showed no effect on binding to TLR3 or in their ability to inhibit TLR3 biological activity when compared to their parent counterparts (data not shown).

Example 2**Determination of TLR3 Antagonist Activity *in vitro***

[0128] The 15 CDR-matured candidates described above were selected as potential human therapeutics and a range of binding and neutralizing activities were determined. The activity assays and results for the four parental Fabs, Fabs 16-19 and 15 CDR-matured Fabs, Fabs 1-15 or their non-germline V-region variants are described below.

Inhibition of NF- κ B and ISRE Signaling Cascade

[0129] 293T cells were grown in DMEM and GlutaMax media (Invitrogen, Carlsbad, CA) supplemented with heat-inactivated FBS and transfected with 30 ng pNF- κ B or ISRE firefly luciferase reporter plasmids, 13.5 ng pcDNA3.1 vector, 5 ng phRL-TK, and 1.5 ng pCDNA encoding FL TLR3 (SEQ ID NO: 2). The phRL-TK plasmid contains the *Renilla* luciferase gene driven by the HSV-1 thymidine kinase promoter (Promega, Madison, WI). TLR3 antibodies were incubated 30-60 min. before addition of poly(I:C) (GE Healthcare, Piscataway, NJ). The plates were incubated 6h or 24h at 37°C before the addition of the Dual-Glo luciferase reagent, and the plates were read on a FLUOstar plate reader. Normalized values (luciferase ratios) were obtained by dividing the firefly RLUs by the *Renilla* RLUs. Upon stimulation with the TLR3 agonist poly (I:C) (1 μ g/ml), the NF- κ B or ISRE signaling cascade stimulated firefly luciferase production was specifically inhibited by incubation of the cells with anti-TLR3 antibodies (0.4, 2.0 and 10 μ g/ml) prior to stimulation. The results for the NF- κ B assays are shown in Fig. 1 and are expressed as % inhibition of the Firefly/*Renilla* ratio with 5465 as the positive control (neutralizing anti-human TLR3 Mab) and an anti-human tissue factor mAb (859) as the human IgG4 isotype control. >50% inhibition was achieved with mAb concentrations 0.4-10 μ g/ml. c1068 and TLR3.7 inhibited about

38% and 8% of TLR3 biological activity at 10 $\mu\text{g/ml}$. Similar results were obtained with the ISRE reporter gene assay (data not shown).

Cytokine Release in BEAS-2B cells

[0130] BEAS-2B cells (SV-40 transformed normal human bronchial epithelial cell line) were seeded in a collagen type I coated dishes and incubated with or without anti-human TLR3 antibodies prior to addition of poly (I:C). Twenty-four hours after treatments, supernatants were collected and assayed for cytokine and chemokine levels using a custom multi-plex bead assay for detection of IL-6, IL-8, CCL-2/MCP-1, CCL5/RANTES, and CXCL10/IP-10. Results are shown in Fig. 2 as % inhibition of the individual cytokine/chemokine following mAb treatment at 0.4, 2.0 and 10 $\mu\text{g/ml}$. 5465 is a positive control; 859 is an isotype control.

Cytokine Release in NHBE cells

[0131] Cytokine release was also assayed in normal human bronchial epithelial (NHBE) cells (Lonza, Walkersville, MD). NHBE cells were expanded and transferred to collagen-coated dishes and incubated for 48 hours after which the media was removed and replenished with 0.2 ml of fresh media. The cells were then incubated with or without anti-human TLR3 mAbs 60 minutes prior to the addition of poly (I:C). Supernatants were collected after 24 hours and stored at -20°C or assayed immediately for IL-6 levels. Results are graphed in Fig. 3 as % inhibition of IL-6 secretion following mAb treatment using doses between 0.001 and 50 $\mu\text{g/ml}$. 5465 is a positive control, 859 is an isotype control. Most mAbs inhibited at least 50% of IL-6 production at <1 $\mu\text{g/ml}$, and achieved 75% inhibition at <5 $\mu\text{g/ml}$.

Cytokine Release in PBMC cells

[0132] Cytokine release was also assayed in human peripheral blood mononuclear cells (PBMC). Whole blood was collected from human donors into heparin collection tubes to which a Ficoll-Paque Plus solution was slowly layered underneath. The tubes were centrifuged and the PBMCs, that formed a white layer just above the Ficoll, were recovered and plated. The PBMCs were then incubated with or without anti-human TLR3 mAbs prior to the addition of 25 $\mu\text{g/ml}$ poly(I:C). After 24 hrs, supernatants were collected and cytokine levels were determined using Luminex technology. Results are graphed in Fig. 4 as cumulative percentage inhibition of IFN- γ , IL-12 and IL-6 using a single dose of mAb (0.4 $\mu\text{g/ml}$) with 5465 is a positive control; hIgG4 is an isotype control.

Cytokine Release in HASM cells

[0133] Briefly, human airway smooth muscle (HASM) cells were incubated with or without anti-human TLR3 mAbs prior to the addition of a synergistic combination of 500 ng/ml poly(I:C) and 10 ng/ml TNF- α . After 24 hrs, supernatants were collected and cytokine levels were determined using Luminex technology. Results are graphed in Fig. 5 as levels of the chemokine CCL5/RANTES using three doses of mAb (0.4, 2 and 10 $\mu\text{g/ml}$). 5465 is a positive control; hIgG4 is an isotype control.

[0134] The results from the *in vitro* assays in human cells confirm the ability of the antibodies of the invention to reduce cytokine and chemokines release as a result of binding to huTLR3.

Example 3

Full-length Antibody Constructs

[0135] The four parental Fabs (candidate nos. 16-19) and 15 progeny Fabs (candidate nos. 1-15) heavy chains were cloned onto a human IgG4 background with a S229P Fc mutation. Candidates 9QVQ/QSV, 10QVQ/QSV, 12QVQ/QSV, 14EVQ or 15EVQ were cloned onto a human IgG4 background with F235A/L236A and S229P Fc mutations.

[0136] The mature full-length heavy chain amino acid sequences are shown in SEQ ID NOs: 90-102 and 218-220 as follows:

Candidate	SEQ ID NO:
16	90
17	91
18	92
19	93

(continued)

	Candidate	SEQ ID NO:
5	1	94
	2	95
	3	96
	4	97
	5, 6, 7	98
10	8	99
	9	100
	10, 11, 12	101
	13, 14, 15	102
	9EVQ	218
15	10EVQ, 12EVQ	219
	14EVQ, 15EVQ	220

[0137] For expression, these heavy chain sequences can include an N-terminal leader sequence such as MAWVWTLL-FLMAAAQSIQA (SEQ ID NO: 103). Exemplary nucleotide sequences encoding the heavy chain of candidates 14EVQ and 15EVQ with a leader sequence and the mature form (without a leader sequence) are shown in SEQ ID NOs: 104 and 105, respectively. Likewise, for expression, the light chain sequences of the antibodies of the invention can include an N-terminal leader sequence such as MGVPTQVLGLLLLWLT DARC (SEQ ID NO: 106). Exemplary nucleotide sequences encoding the light chain of codon optimized candidate 15 with a leader sequence and the mature form (without a leader sequence) are shown in SEQ ID NOs: 107 and 108, respectively.

Example 4

Characterization of Anti-TLR3 mAb binding

[0138] EC₅₀ values for the binding of the mAbs to human TLR3 extracellular domain (ECD) were determined by ELISA. Human TLR3 ECD protein was diluted to 2 µg/ml in PBS and 100 µl aliquots were dispensed to each well of a 96-well plate (Corning Inc., Acton, MA). After overnight incubation at 4°C, the plate was washed 3 times in wash buffer consisting of 0.05% Tween-20 (Sigma-Aldrich) in PBS. The wells were blocked with 200 µl blocking solution consisting of 2% I-Block (Applied Biosystems, Foster City, CA) and 0.05% Tween-20 in PBS. After blocking for 2 hours at room temperature the plate was washed 3 times followed by addition of serial dilutions of the anti-TLR3 mAb candidates 1 to 19 in blocking buffer. The anti-TLR3 mAbs were incubated for 2 hours at room temperature and washed 3 times. This was followed by addition of a peroxidase-conjugated sheep anti-human IgG (GE Healthcare, Piscataway, NJ) diluted 1:4000 in blocking buffer, incubated for 1 hour at room temperature followed by 3 washes in wash buffer. Binding was detected by 10-15 minute incubation in TMB-S (Fitzgerald Industries International, Inc., Concord, MA). The reaction was stopped with 25 µl 2N H₂SO₄ and absorbance read at 450 nm with subtraction at 650 nm using a SPECTRA Max spectrophotometer (Molecular Devices Corp., Sunnyvale, CA). EC₅₀ values were determined by non-linear regression using GraphPad Prism software (GraphPad Software, Inc., San Diego, CA).

[0139] EC₅₀ values were determined for binding to huTLR3 (Table 4) by incubating with 100 µl of 4-fold serial dilutions of mAbs from 2.5 µg/ml to 0.6 pg/ml. An anti-human tissue factor mAb 859 and hu IgG4κ were included as negative controls.

Table 4

Candidate no.	EC ₅₀ (ng/ml)
1	17.18
2	53.12
3	23.42
4	12.77
5	19.94
6	19

EP 2 350 304 B1

(continued)

Candidate no.	EC50 (ng/ml)
7	16.13
8	18.58
9	22.61
10	15.84
11	26.33
12	25.59
13	23.51
14	33.59
15	32.64
16	43.66
17	13.8
18	9.68
19	66.54

[0140] Binding affinity for huTLR3 ECD was also determined by Biacore analysis. The data (not shown) indicated that the mAbs 1-19 had a K_d for huTLR3 ECD of less than 10⁻⁸ M.

Example 5

Competitive Epitope Binding

[0141] Epitope binding experiments were performed to determine the anti-TLR3 antibody competition groups or "epitope bins".

[0142] For competitive ELISA, 5 μ l (20 μ g/ml) of purified human TLR3 ECD protein generated as described in Example 1 was coated on MSD HighBind plate (Meso Scale Discovery, Gaithersburg, MD) per well for 2 hr at room temperature. 150 μ l of 5% MSD Blocker A buffer (Meso Scale Discovery) was added to each well and incubated for 2 hr at room temperature. Plates were washed three times with 0.1 M HEPES buffer, pH 7.4, followed by the addition of the mixture of labeled anti-TLR3 mAb with different competitors. Labeled antibodies (10 nM) were incubated with increasing concentrations (1 nM to 2 μ M) of unlabeled anti-TLR3 antibodies, and then added to the designated wells in a volume of 25 μ l mixture. After 2-hour incubation with gentle shaking at room temperature, plates were washed 3 times with 0.1 M HEPES buffer (pH 7.4). MSD Read Buffer T was diluted with distilled water (4-fold) and dispensed at a volume of 150 μ l/well and analyzed with a SECTOR Imager 6000. Antibodies were labeled with MSD Sulfo-Tag™ NHS-ester according to manufacturer's instructions (Meso Scale Discovery).

[0143] The following anti-TLR3 antibodies were evaluated: mAbs 1-19 obtained from MorphoSys Human Combinatorial Antibody Library (shown in Table 3a); c1068 (described in WO06/060513A2), c1811 (rat anti-mouse TLR3 mAb produced by a hybridoma generated from rats immunized with mouse TLR3 protein), TLR3.7 (eBiosciences, San Diego, CA, cat no 14-9039) and IMG-315A (generated against human TLR3 amino acids 55-70 (VLNLTHNQLRRLPAAN) from Imgenex, San Diego, CA). For mAbs 9, 10, 12, 14 and 15, variants 9QVQ/QSV, 10QVQ/QSV, 12QVQ/QSV, 14EVQ or 15EVQ were used in this study.

[0144] Based on competition assays, anti-TLR3 antibodies were assigned to five distinct bins. Bin A: mAbs 1, 2, 13, 14EVQ, 15EVQ, 16, 19; Bin B: mAbs 3, 4, 5, 6, 7, 8, 9QVQ/QSV, 10QVQ/QSV, 11, 12QVQ/QSV, 17, 18; Bin C: antibody Imgenex IMG-315A; Bin D: antibodies TLR3.7, c1068; and Bin E: antibody c1811.

Example 6

Epitope Mapping

[0145] Representative antibodies from distinct epitope bins as described in Example 5 were selected for further epitope mapping. Epitope mapping was performed using various approaches, including TLR3 segment swapping experiments,

mutagenesis, H/D exchange and *in silico* protein-protein docking (The Epitope Mapping Protocols, Methods in Molecular Biology, Volume 6, Glen E. Morris ed., 1996).

[0146] TLR3 segment swapping. TLR3 human-mouse chimeric proteins were used to locate gross antibody binding domains on TLR3. The human TLR3 protein extracellular domain was divided into three segments (aa 1-209, aa 210-436, aa 437-708 according to amino acid numbering based on human TLR3 amino acid sequence, GenBank Acc. No. NP_003256). MT5420 chimeric protein was generated by replacing human TLR3 amino acids 210-436 and 437-708 by corresponding mouse amino acids (mouse TLR3, GenBank Acc. No. NP_569054, amino acids 211-437 and 438-709). The MT6251 chimera was generated by replacing human amino acids at positions 437-708 by mouse TLR3 amino acids (mouse TLR3, GenBank Acc. No. NP_569054, amino acids 438-709). All constructs were generated in the pCEP4 vector (Life Technologies, Carlsbad, CA) using standard cloning procedures. The proteins were transiently expressed in HEK293 cells as V5-His6 C-terminal fusion proteins, and purified as described in Example 1.

mAb c1068. mAb c1068 bound human TLR3 ECD with high affinity but did not bind well to murine TLR3. c1068 lost its ability to bind to both MT5420 and MT6251, demonstrating that the binding site was located within the amino acids 437-708 of the WT human TLR3 protein.

mAb 12QVQ/QSV. mAb 12QVQ/QSV bound both chimeras, indicating that the binding site for mAb 12QVQ/QSV was located within the amino acids 1-209 of the human TLR3 protein having a sequence shown in SEQ ID NO:2.

[0147] *In silico* protein-protein docking. The crystal structure of mAb 15EVQ (see below) and the published human TLR3 structure (Bell et al., J. Endotoxin Res. 12:375-378, 2006) were energy minimized in CHARMM (Brooks et al., J. Computat. Chem. 4:187-217, 1983) for use as the starting models for docking. Protein docking was carried out with ZDOCKpro 1.0 (Accelrys, San Diego, CA), which is equivalent to ZDOCK 2.1 (Chen and Weng, Proteins 51: 397-408, 2003) with an angular grid of 6 degrees. Known N-linked glycosylation site Asn residues in human TLR3 (Asn 52, 70, 196, 252, 265, 275, 291, 398, 413, 507 and 636) (Sun et al., J. Biol. Chem. 281:11144-11151, 2006) were blocked from participating in the antibody-antigen complex interface by an energy term in the ZDOCK algorithm. 2000 initial poses were output and clustered and the docking poses were refined and rescored in RDOCK (Li et al., Proteins 53:693-707, 2003). The 200 poses with the highest initial ZDOCK scores and 200 top RDOCK poses were visually inspected.

[0148] Crystallization of mAb 15EVQ was carried out by the vapor-diffusion method at 20°C (Benvenuti and Mangani, Nature Protocols 2:1633-51, 2007). The initial screening was set up using a Hydra robot in 96-well plates. The experiments were composed of droplets of 0.5 µl of protein solution mixed with 0.5 µl of reservoir solution. The droplets were equilibrated against 90 µl of reservoir solution. The Fab solution in 20 mM Tris buffer, pH 7.4, containing 50 mM NaCl was concentrated to 14.3 mg/ml using Amicon Ultra-5 kDa cells. The screening was performed with the Wizard I & II (Emerald BioSystems, Bainbridge Island, WA) and in-house crystallization screens.

[0149] X-ray diffraction data were collected and processed using the Rigaku MicroMax™-007HF microfocus X-ray generator equipped with an Osmic™ VariMax™ confocal optics, Saturn 944 CCD detector, and an X-stream™ 2000 cryocooling system (Rigaku, Woodlands, TX). Diffraction intensities were detected over a 270° crystal rotation with the exposure time of 120 s per half-degree image. The X-ray data were processed with the program D*TREK (Rigaku). The structure was determined by the molecular replacement method using the program Phaser or CNX (Accelrys, San Diego, CA). Atomic positions and temperature factors were refined with REFMAC using all data in the resolution range 15-2.2 Å for mAb 15 and 50-1.9 Å for mAb 12. Water molecules were added at the ($F_o - F_c$) electron density peaks using the cut-off level of 3σ . All crystallographic calculations were performed with the CCP4 suite of programs (Collaborative Computational Project, Number 4, 1994. The CCP4 suite: programs for protein crystallography. Acta Crystallogr. D50:760-763). Model adjustments were carried out using the program COOT (Emsley et al., Acta Crystallogr. D60:2126-2132, 2004).

[0150] The resolved crystal structure of mAb 15EVQ showed that the antibody combining site was characterized by a number of negatively charged residues in the heavy chain (D52, D55, E99, D106 and D109). Thus, recognition between mAb 15EVQ and TLR3 most likely involved positively charged residues. The protein-protein docking simulations performed suggested that two large patches on TLR3 involving multiple positive charge residues showed good complementarity to the antibody. The residues on TLR3 in the interface of the TLR3 - anti-TLR3 antibody simulated complexes were R64, K182, K416, K467, Y468, R488, R489 and K493.

[0151] Mutagenesis studies. Single and combination point mutations were introduced into surface residues of TLR3 ECD in the regions identified above to contain the epitopes of mAb 12 and mAb 15EVQ and the mutant proteins were tested for antibody binding.

[0152] The nucleotide sequence encoding human TLR3 amino acids 1-703 (the ECD), (SEQ ID NO: 4; GenBank accession number NP_003256), was cloned using standard protocols. All mutants were generated by site directed mutagenesis using the Stratagene Quickchange II XL kit (Stratagene, San Diego, CA) according to the manufacturer's protocol, using the oligonucleotides shown in Table 5a. Mutations were verified by DNA sequencing. The proteins were expressed under a CMV promoter as C-terminal His-tag fusions in HEK293 cells, and purified as described in Example 1.

Table 5a. Oligonucleotides used for site-directed mutagenesis. Sequences of the sense oligonucleotides are shown. The anti-sense oligonucleotides with complementary sequences were used in the mutagenesis reaction.

Variant	Oligo	SeqID NO:
R64E	5'CCTTACCCATAATCAACTCGAGAGATTACCGCCGCCAAC 3'	136
K182E	5'CAAGAGCTTCTATTATCAACAATGAGATTCAAGCGCTAAAAAGTGAAG 3'	137
K416E	5'CCTTACACATACTCAACCTAACCGAGAAATAAATCTCAAAAATAG 3'	138
K467E/Y468A	5'GAAATCTATCTTTCTACAACGAGGCCCTGCAGCTGACTAGGAATC 3'	139
R488/R489/K493E	5'GCCTTCAACGACTGATGCTCGAGGAGGTGGCCCTTGAGAAATGTGATAGCTCTCCTTC 3'	140
T472S/R473T/N474S	5'GTACCTGCAGCTGTCTACGAGCTCCTTTGCCCTTGGTCCC 3'	141
N196A	5'GAAGAACTGGATATCTTTGCCGCTTCATCTTTAAAAAATTAGATTG 3'	169
Q167A	5'GTCATCTACAAAAATTAGGAAGTGGGTTTCAGCTGGAAAAATCTCC 3'	170
K163E	5'CTCATAATGGCTGTCTATCTACAGAATTAGGAACTCAGGTTTCAGC 3'	171
K147E	5'GAAAAATTAAAAATAATCCCTTTGTCAAGCAGGAGAAATTTAATCACATTAGATCTGTC 3'	172
K145E	5'GAAAAATTAAAAATAATCCCTTTGTGCGAGCAGAAATTTAATCACATTAG 3'	173
V144A	5'CAGAAAAATTAAAAATAATCCCTTTGCAAGCAGAAAGAAATTTAATCACATTAG 3'	174
N140A	5'CCAACCTCAATCCAGAAAAATTAAAGCTAATCCCTTTGTCAAGCAGAAG 3'	175
D116R	5'CAATGAGCTATCTCAACCTTCTCGTAAACCTTTGCCCTTCTGCAC 3'	176
D536K	5'GTCTTGAGAACTAGAAATTCGAAGTTGCAGCATAACAACCTTAGCAC 3'	177
D536A	5'CTTGAGAACTAGAAATTCGCAATTCGCAATTCGAGCATAACAACCTTAGCAC 3'	178
K619E	5'CTAAAGTCATTGAACCTTCAGGAGAAATCTCATAACATCCGTTG 3'	179
K619A	5'CTCTAAAGTCATTGAACCTTCAGGCGAATCTCATAACATCCGTTGAG 3'	180
E570R	5'CCACATCCTTAACCTTGAGGTCCACCGCTTTGACGAG 3'	181
N541A	5'GAAATTCGATTTGCAGCATAACGCTTAGCACGGCTCTGGAAC 3'	182
Q538A	5'GAGAAACTAGAAATTCGATTTGGCGCATAACAACCTTAGCACGGC 3'	183
H539E	5'CTAGAAATTCGATTTGCAGGAAACAACCTTAGCACGGCTCTG 3'	184
H539A	5'CTAGAAATTCGATTTGCAGGCTAACAACTTAGCACGGCTCTG 3'	185
N517A	5'CATTCTGGATCTAAGCAACAACGCCCATAGCCCAACATAAATGATGAC 3'	186
Y465A	5'GAAAAATATTTTCGAAATCTATCTTTCCGCCCAACAAGTACCTGCAGCTGAC 3'	187

Variant	Oligo	SeqID NO:
R488E	5'GCCTTCAACGACTGATGCTCGAAAGGGTGGCCCTTAAAAATG 3'	188
R489E	5'CTTCAACGACTGATGCTCCGAGAGGTGGCCCTTAAAAATGTGG 3'	189
K467E	5'CGAAATCTATCTTTCCCTACAACGAGTACCTGCAGCTGACTAG 3'	190

[0153] Binding assays. The binding activity of mAb 12QVQ/QSV and mAb 15EVQ to human TLR3 and generated variants was evaluated by ELISA. To expedite the process, mutants in the predicted mAb 15EVQ binding site were co-expressed in HEK cells by co-transfection of TLR3 ECD mutant containing a C-terminal His tag with mAb 12QVQ/QSV, followed by purification by metal affinity chromatography. The recovered sample was a complex of the TLR3 mutant with mAb 12. This approach was feasible because the mAb 12QVQ/QSV and mAb 15EVQ binding sites are distant from one another; and thus, point mutations at one site are unlikely to affect the epitope at the other site. These complexes were used in the ELISA binding assays. 5 μ l per well of 20 μ g/ml wild type TLR3 ECD or mutant proteins in PBS were coated on an MSD HighBind plate (Meso Scale Discovery, Gaithersburg, MD). The plates were incubated at room temperature for 60 min and blocked overnight in MSD Blocker A buffer (Meso Scale Discovery, Gaithersburg, MD) at 4°C. The following day the plates were washed and the MSDSulfo-tag labeled mAb 15EVQ added at concentrations from 500 pM to 1 pM for 1.5 hours. After washes the labeled antibody was detected using MSD Read Buffer T and the plates were read using a SECTOR Imager 6000. To evaluate the binding activity of mAb 12QVQ/QSV to human TLR3 and variants, co-expression was carried out with mAb 15EVQ and binding ELISAs were performed as described for mAb 15EVQ, except that the detecting antibody was labeled mAb 12QVQ/QSV.

mAb 12QVQ/QSV: The binding site for mAb 12QVQ/QSV was located within the amino acids 1-209 of the human TLR3 protein as determined in the segment swap studies. The following TLR3 mutants were evaluated: D116R, N196A, N140A, V144A, K145E, K147E, K163E, and Q167A. The wild type TLR3 and V144A mutant showed comparable binding to mAb 12QVQ/QSV (Figure 6A). The antibody did not bind to TLR3 D116R mutant and had significantly reduced binding affinity to the K145E mutant. Thus, residues D116 and K145 which are closely apposed on the surface of TLR3 were identified as key epitope sites for mAb 12QVQ/QSV (Figure 7A).

[0154] The two critical residues of the mAb 12QVQ/QSV binding epitope were located near the face of the dsRNA binding site at the N-terminal segment of the TLR3 ectodomain (Pirher, et al., Nature Struct. & Mol. Biol., 15:761-763, 2008). The complete epitope will contain other residues in the neighboring regions, which were not revealed by mutational analyses performed. Not wishing to be bound to any particular theory, it is believed that binding of mAb 12QVQ/QSV on its TLR3 epitope may directly or indirectly interfere with dsRNA binding on TLR3 ectodomain, thereby disrupting receptor dimerization and activation of downstream signaling pathways.

mAb 15EVQ: The following TLR3 mutants were evaluated: R64E, K182E, K416E, Y465A, K467E, R488E, R489E, N517A, D536A, D536K, Q538A, H539A, H539E, N541A, E570R, K619A, K619E, a double mutant K467E/Y468A, a triple mutant T472S/R473T/N474S, and a triple mutant R488E/R489E/K493E. The wild type TLR3, the R64E, K182E, K416E mutants and the triple mutant T472S/R473T/N474S showed comparable binding to mAb 15EVQ (Figure 6B and Table 5b). The antibody did not bind to TLR3 mutants K467E, R489E, K467E/Y468A and R488E/R489E/K493E (Figure 6B and 6C). The remaining variants showed intermediate binding with the R488E having the greatest effect. All of these mutants bound to mAb 12QVQ/QSV. These results showed that residues K467 and R489 were critical determinants of the mAb 15EVQ epitope. Residue R488 also contributed to the epitope. These residues were closely apposed on the same surface of TLR3 (**Figure 7A**). The results also showed that residues Y465, Y468, N517, D536, Q538, H539, N541, E570, and K619, all on the same surface as K467, R488 and R489, contributed to the epitope. This conclusion was further supported by the H/D exchange studies with mAb 15EVQ. Figure 7A shows binding epitope sites for mAbs 12QVQ/QSV and 15EVQ (black) and C1068 mAb (grey) superimposed on the structure of human TLR3. The epitope for mAb 15EVQ covers residues Y465, K467, Y468, R488, R489, N517, D536, Q538, H539, N541, E570, and K619.

[0155] H/D Exchange studies. For H/D exchange, the procedures used to analyze the antibody perturbation were similar to that described previously (Hamuro et al., J. Biomol. Techniques 14:171-182, 2003; Horn et al., Biochemistry 45:8488-8498, 2006) with some modifications. Recombinant TLR3 ECD (expressed from Sf9 cells with C-terminal His-tag and purified) was incubated in a deuterated water solution for predetermined times resulting in deuterium incorporation at exchangeable hydrogen atoms. The deuterated TLR3 ECD was captured on a column containing immobilized mAb 15EVQ and then washed with aqueous buffer. The back-exchanged TLR3 ECD protein was eluted from the column and localization of deuterium containing fragments was determined by protease digestion and mass spec analysis. As a reference control, TLR3 ECD sample was processed similarly except it was exposed to deuterated water only after capture on the antibody column and then washed and eluted in the same manner as the experimental sample. Regions bound to the antibody were inferred to be those sites relatively protected from exchange and thus contain a higher fraction of deuterium than the reference TLR3 ECD sample. About 80% of the protein could be mapped to specific peptides. Maps of H/D exchange perturbation of TLR3 ECD by mAb 15EVQ are shown in Figure 7B. Only the segment of TLR3 around the portion affected by mAb 15EVQ is shown for clarity. The remainder of the protein extending to the amino and carboxyl termini of TLR3 ECD was not affected appreciably.

[0156] The H/D exchange studies identified peptide segments ⁴⁶⁵YNKYLQL₄₇₁, ⁵¹⁴SNNNIANINDDML₅₂₆ and ⁵²⁹LEKL₅₃₂ of SEQ ID NO: 2 as regions where exchange on TLR3 was particularly altered by binding to mAb 15EVQ. By its nature, H/D exchange is a linear mapping method and usually cannot define which residues within the peptide segment are most affected by antibody binding. However, the extensive overlap between the H/D exchange and mutational results gives added confidence that the surface shown in Figure 7A is the binding site for mAb 15. This binding site was in same linear amino acid sequence region as previously described for mAb c1068 (PCT Publ. no. WO06/060513A2) but it was found to be located on a completely non-overlapping surface (Figure 7A) in agreement with the lack of cross-competition between these antibodies.

[0157] The mAb 15EVQ binding epitope was spatially proximal to the dsRNA binding site at the C-terminal segment on TLR3 (Bell et al., Proc. Natl. Acad. Sci. (USA) 103: 8792-8797, 2006; Ranjith-Kumar et al., J Biol Chem, 282: 7668-7678, 2007; Liu et al., Science, 320: 379-381, 2008). Not wishing to be bound to any particular theory, it is believed that binding of mAb 15EVQ on its TLR3 epitope causes steric clashes with a ligand dsRNA molecule and/or the dimer partner, preventing ligand binding and ligand-induced receptor dimerization.

Table 5b.

Variant	mAb 15		Variant	mAb 12
wt TLR3 ECD	+++		wt TLR3 ECD	+++
R64E	+++		D116R	-
K182E	+++		N140A	++
K416E	+++		V144A	+++
Y465A	++		K145E	+
K467E	-		K147E	++
R488E	+		K163E	++
R489E	-		Q167A	++
N517A	++		N196A	++
D536K	++			
D536A	++			
Q538A	++			
H539E	++			
H539A	++			
N541A	++			
E570R	++			
K619E	++			
K619A	++			
K467E/Y468A	-			
R488/R489/K493E	-			
T472S/R473T/N474S	+++			

Example 7

Generation of variants with enhanced thermal stability

[0158] Structure-based engineering was conducted to generate antibody variants with increased thermal stability, with simultaneous efforts to maintain the biological activity and minimize immunogenicity.

[0159] mAb 15EVQ was selected for engineering. To minimize immunogenicity, only germline mutations predicted to be beneficial based upon structural considerations were pursued. The VL and VH sequences of mAb 15EVQ (SEQ ID NO: 41 and SEQ ID NO: 216, respectively) were aligned with the human germline genes using BLAST searches. The

closest germline sequences identified were GenBank Acc. No. AAC09093 and X59318 for VH and VL, respectively. The following differences were identified between the germline VH, VL and those of the mAb 15EVQ VH and VL sequences: (VH) V34I, G35S, F50R, A61S, and Q67H; (VL) G30S, L31S, and A34N. The identified sequence differences were mapped onto the crystal structure of the mAb 15EVQ, and residues predicted to alter packing and interface interactions were selected for engineering. Based upon the crystal structure of the antibody (see Example 6), potential structure destabilizing residues were identified. (1) A small enclosed cavity was identified in the core of VH near V34. This cavity was large enough to accommodate a slightly larger sidechain such as Ile. (2) E99 of VH CDR3 was buried at the VH/VL interface without a H-bonding network. The negatively charged carboxylate group of E99 was in a generally hydrophobic environment with mostly van der Waals (vdw) contacts to neighboring residues. Burying a charge group is usually energetically unfavorable and thus has destabilizing effect. (3) F50 of VH is a VH/VL interface residue. Its aromatic sidechain is bulky and thus may have negative impact upon the pairing. H-bonding and vdw packing networks for the Fv were calculated and visually inspected in Pymol

([www://_pymol_org](http://www.pymol.org)). Buried cavities in the VH and VL domains were computed by Caver (Petrek et al., BMC Bioinformatics, 7:316, 2006). All molecular graphics figures were prepared in Pymol. Mutations were made to the expression vectors encoding Fab fragments or IgG4 full human antibodies generated as described in Example 3 using standard cloning techniques using Quick Change II XL Site Directed Mutagenesis Kit (Stratagene, San Diego, CA), Change-IT Multiple Mutation Site Directed Mutagenesis Kit (USB Corporation, Cleveland, OH) or Quick Change II Site Directed Mutagenesis Kit (Stratagene, San Diego, CA). The reactions were performed according to each manufacturer's recommendations. The obtained clones were sequenced for verification, and the resulting engineered variants were named mAbs 15-1 - 15-9. A listing of the SEQ ID NOs: for the CDRs, variable regions of light and heavy chains and full length heavy and light chains for mAb 15EVQ and its engineered variants is shown in Table 6. Table 7 shows primers for generation of each variant.

Table 6.

Candidate no:	SEQ ID NO:									
	HCDR1	HCDR2	HCDR3	LCDR1	LCDR2	LCDR3	LV	HV	Heavy IgG4	Light chain
15	111	112	84	109	110	113	41	216	220	156
15-1	111	114	84	109	110	113	41	124	130	156
15-2	115	112	84	109	110	113	41	125	131	156
15-3	116	112	84	109	110	113	41	126	132	156
15-4	111	117	84	109	110	113	41	127	133	156
15-5	116	118	84	109	110	113	41	128	134	156
15-6	116	112	119	109	110	113	41	129	135	156
15-7	111	112	84	120	110	113	122	42	102	157
15-8	111	112	84	121	110	113	123	42	102	158
15-9	116	118	119	109	110	113	41	159	160	156

[0160] Binding of mAbs 15-1 - 15-9 to TLR3 was evaluated by ELISA immunoassay. Human TLR3 ECD (100 μ l of 2 μ g/ml TLR3-ECD) was bound to a black Maxisorb plate (eBioscience) overnight at 4°C. The plates were washed and blocked, and diluted antibodies were aliquoted at 50 μ l per well in duplicate onto the wells. The plate was incubated at RT for 2 hours shaking gently. Binding was detected using luminescence POD substrate (Roche Applied Science, Mannheim, Germany, Cat. No. 11 582 950 001) and goat anti-human Fc:HRP (Jackson ImmunoResearch, West Grove, PA, Cat. No. 109-035-098) and the plate was read in a SpectraMax plate reader (Molecular Devices, Sunnyvale, CA).

Table 7.

Candidate no:	Mutants	Primers	Seq ID NO:	Resulting palsemid #	Mutagenesis template palsemid #
15-1	HC: F50R	GCCTGGAGTGGATGGCCGGGATCGACCCAGCG	142	5042	p4595
		CGCTGGGGTCGATCCGGGCCCATCCACTCCAGGC	143		
15-2	HC: V341	AGAGGTAACCTCCCGTTGCGG	144	5046	p4584
		GCATCTGGCGCACCCAGCCGATCCAGTAGTTGGTGAA G	145		
15-3	HC: V341/G35S	AGAGGTAACCTCCCGTTGCGG	146	5045	p4584
		GCATCTGGCGCACCCAGCTGATCCAGTAGTTGGTGAA G	147		
15-4	HC: A61S/Q67H	AGAGGTAACCTCCCGTTGCGG	144	5048	p4584
		CGCTGATGTCACGTGCCCTGGAAGCTAGGGCTGTA GTTGGTGTAG	148		
15-5	HC: F50R/V341/G35S/A61S/Q67H	CTTCACCAACTACTGGATCAGCTGGGTGCGCCAGATGC	149	5069	p5042
		CGCTGATGTCACGTGCCCTGGAAGCTAGGGCTGTA GTTGGTGTAG	148		
15-6	HC: V341/G35S/E99Q	CGCCATGTACTACTGCGCCCGCCAGCTGTACCAGGGC TAC	150	5070	p5045
		GTAGCCCTGGTACAGCTGGCGGGCGCAGTAGTACATG GCG	151		
15-7	LC: G30S/L31S	GCCAGCCAGCATCAGCAGCTACCTGGCCTGGTACC AGC	152	5043	p4595
		GCTGGTACCAGGCCAGGTAGCTGCTGATGCTCTGGCT GGC	153		
15-8	LC: A34N	AGAGGTAACCTCCCGTTGCGG	144	5047	p4588
		CGGGCTTCTGCTGGTACCAGTTTCAGGTAGCTGCTGATG CTCTG	154		

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(continued)

Candidate no:	Mutants	Primers	Seq ID NO:	Resulting palsmid #	Mutagenesis template oalsmid #
15-9	HC: F50RV34I/G35S /A61S/Q67H/E99Q	CGCCATGTACTACTGCGCCCCGCCAGCTGTACCAGGGC TAC	150	5097	p5069*
		GTAGCCCTGGTACAGCTGGCGGGCGCAGTAGTACATG GCG	151		
		*p5069 as a single gene for heavy chain. Variable reagon of p5069 swaped to p5070 backbone			

[0161] DSC experiments were performed on a MicroCal's Auto VP-capillary DSC system (MicroCal, LLC, Northampton, MA) in which temperature differences between the reference and sample cells were continuously measured, and calibrated to power units. Samples were heated from 10 °C to 95 °C at a heating rate of 60 °C/hour. The pre-scan time was 15 minutes and the filtering period was 10 seconds. The concentration used in the DSC experiments was about 0.5 mg/ml. Analysis of the resulting thermograms was performed using MicroCal Origin 7 software (MicroCal, LLC).

[0162] The thermal stability (T_m) of the generated variants was measured by DSC (Table 8). Binding of the antibody variants to TLR3 was comparable to that of the parental antibody.

Table 8. Summary of melting temperatures (T_m) of the variants and rationale for making them.

Candidate no:	Mutations		Rationale	T_m (°C)	ΔT_m (°C)
15EVQ		WT		64.7	0
15-1	HV	F50R	VH/VL interface	69.3	4.6
15-2	HV	V34I	VH core packing	66.9	2.2
15-3	HV	V34I/G35S	H-bonding, VH core packing	71.2	6.5
15-4	HV	A61S/Q67H	VH/VL packing, VH surface charge distribution	65.4	0.7
15-5	HV	F50R/V34I/G35S/A61S/Q67H	VH/VL interface, H-bonding, VH core packing, VH/VL packing, VH surface charge distribution	76.2	11.5
15-6	HV	V34I/G34S/E99Q	H-bonding, VH core packing, removal of buried charge	75	10.3
15-7	LV	G30S/L31S	L-CDR1 surface polar residues	63.1	-1.6
15-8	LV	A34N	VL/VH interface	64	-0.7
15-9	HV	F50R/V34I/G35S/A61S/Q67H/E99Q	VH/VL interface, H-bonding, VH core packing, VH/VL packing, VH surface charge distribution, removal of buried charge	76	11.3

Example 8

Generation of a surrogate anti-TLR3 antibody

[0163] A chimeric antagonistic rat/mouse anti-mouse TLR3 antibody, herein named mAb 5429 was generated to evaluate effects of inhibiting TLR3 signaling in various *in vivo* models, as the humanized antibodies generated in Example 1 did not have sufficient specificity or antagonist activity for mouse TLR3. The surrogate chimeric mAb 5429 as well as its parent rat anti-mouse TLR3 antibody c1811 inhibited mouse TLR3 signaling *in vitro*, and *in vivo*, and ameliorated pathogenic mechanisms in several disease models in the mouse.

[0164] Data discussed below suggests a role for TLR3 in the induction and perpetuation of detrimental inflammation, and contribute to the rationale for the therapeutic use of TLR3 antagonists and TLR3 antibody antagonists, for example acute and chronic inflammatory conditions including hypercytokinemia, asthma and airway inflammation, inflammatory bowel diseases and rheumatoid arthritis, viral infections, and type II diabetes.

Generation of the surrogate mAb 5429

[0165] CD rats were immunized with recombinant murine TLR3 ectodomain (amino acids 1-703 of seq ID NO: 162, GenBank Acc. No. NP_569054) generated using routine methods. Lymphocytes from two rats demonstrating antibody titers specific to murine TLR3 were fused to FO myeloma cells. A panel of monoclonal antibodies reactive to murine TLR3 were identified and tested for *in vitro* antagonist activity in the murine luciferase reporter and murine embryonic fibroblast assays. The hybridoma line C1811A was selected for further work. Functional variable region genes were sequenced from mAb c1811 secreted by the hybridoma. Cloned heavy chain and light chain variable region genes were then respectively inserted into plasmid expression vectors that provided coding sequences for generating a chimeric Rat/Balb C μ lgG1/ κ mAb designated as mAb 5429 using routine methods. The antibodies were expressed as described in Example 3. The amino acid sequences of the mAb 5429 heavy and light chain variable regions are shown in SEQ ID NO:164 and SEQ ID NO: 163, respectively, and the heavy and light chain full length sequences are shown in SEQ ID

NO:166 and SEQ ID NO: 165, respectively. The heavy and light chain full length sequences of mAb c1811 are shown in SEQ ID NO: 168 and SEQ ID NO: 167, respectively.

Characterization of mAb 5429

[0166] mAb 5429 was characterized in a panel of *in vitro* assays for its neutralizing ability on TLR3 signaling. The activity assays and results are described below.

Murine Luciferase Reporter Gene Assay

[0167] The murine TLR3 cDNA (SEQ ID NO: 161, GenBank Acc. No: NM_126166) was amplified by PCR from murine spleen cDNA (BD Biosciences, Bedford, MA), and cloned into the pCEP4 vector (Life Technologies, Carlsbad, CA) using standard methods. 200 μ l HEK293T cells were plated in 96 well white clear-bottom plates at a concentration of 4×10^4 cells/well in complete DMEM, and used the following day for transfections using Lipofectamine 2000 (Invitrogen Corp., Carlsbad, CA) using 30 ng pNF- κ B firefly luciferase (Stratagene, San Diego, CA) or 30 ng pISRE firefly luciferase (BD Biosciences, Bedford, MA), 5 ng phRL-TK control Renilla luciferase (Promega Corp., Madison, WI) reporter plasmids, 1.5 ng pCEP4 encoding the full-length murine TLR3, and 13.5 ng empty pcDNA3.1 vector (Life Technologies, Carlsbad, CA) to bring the total DNA amount to 50 ng/well. 24 hours post-transfection, the cells were incubated for 30 minutes to 1 hour at 37°C with the anti-murine TLR3 antibodies in fresh serum-free DMEM before the addition of 0.1 or 1 μ g/ μ l poly(I:C). The plates were harvested after 24 hours using the Dual-Glo Luciferase Assay System (Promega, Madison, WI). The relative light units were measured using a FLUOstar OPTIMA multi-detection reader with OPTIMA software (BMG Labtech GmbH, Germany). Normalized values (luciferase ratios) were obtained by dividing the firefly relative light units (RLUs) by the Renilla RLUs. mAb 5429 as well as its parent mAb c1811 and mAb 15 (Table 3a) reduced poly(I:C) - induced NF- κ B and ISRE activation in a dose-dependent fashion (Figure 8A and 8B), demonstrating their abilities to antagonize the activity of TLR3. IC50s measured in the ISRE assay were 0.5, 22, and 0.7 μ g/ml for mAb 5249, mAb 15 and mAb c1811, respectively.

Murine Embryonic Fibroblast (MEF) Assay

[0168] C57BL/6 MEF cells were obtained from Artis Optimus (Opti-MEF™ C57BL/6 - 0001). The cells were plated in 96-well flat bottom plates (BD Falcon) at 20,000 cells/well in 200 μ l MEF media (DMEM with glutamax, 10% heat inactivated-FBS, 1x NEAA, and 10 μ g/ml gentamycin). All incubations were done at 37°C/5%CO₂. 24 hours after plating, mAb 5429 or mAb c1811 were added into wells. The plates were incubated with the mAbs for 1hr, after which Poly(I:C) was added at 1 μ g/ml in each well. The supernatants were collected after a 24-hour incubation. Cytokine levels were determined using a bead kit (Invitrogen Corp., Carlsbad, CA) to detect CXCL10/IP-10 following manufacturer's protocol. The results were graphed using GraphPad Prism Software. Both antibodies reduced poly(I:C)-induced CXCL10/IP-10 levels in a dose-dependent manner, demonstrating the abilities of these antibodies to antagonize endogenous TLR3 and inhibit TLR3 signaling (Figure 9).

Flow Cytometry- Surface Staining

[0169] C57BL/6 and TLR3 knockout (TLR3KO) (C57BL/6 background; female, 8-12 weeks of age, Ace Animals, Inc.), 10 per group, were dosed intraperitoneally with 1 ml of 3% Thioglycollate medium (Sigma) and 96 hrs later, the mice were euthanized and the peritoneum from each mouse was lavaged with 10 ml sterile PBS. Thioglycollate-elicited peritoneal macrophages were resuspended in PBS and cell viability was assessed using Trypan Blue staining. Cells were pelleted by centrifugation and resuspended in 250 μ l FACS Buffer (PBS -Ca²⁺-Mg²⁺, 1% heat-inactivated FBS, 0.09% Sodium Azide) and were kept on wet ice. The CD16/32 reagent (eBioscience) was used at 10 μ g/10⁶ cells for 10 minutes to block Fc Receptors on the macrophages. The cells were distributed at 10⁶ cells in 100 μ l/well for surface staining. Alexa-Fluor 647 (Molecular Probes)-conjugated mAb c1811 and mAb 1679 (rat anti-mouse TLR3 antibody that had no TLR3 specificity, and thus used as an isotype control) were added at 0.25 μ g/10⁶ cells and incubated on ice in the dark for 30 minutes. The cells were washed and resuspended in 250 μ l of FACS Buffer. The viability stain, 7-AAD (BD Biosciences, Bedford, MA), was added at 5 μ l/well no more than 30 minutes before acquisition of samples on FACS Calibur to detect a dead cell population. Samples were collected by the FACS Calibur using Cell Quest Pro Software. FCS Express was used to analyze the collected data by forming histograms.

[0170] The binding of mAb c1811 to murine thioglycollate-elicited peritoneal macrophages from C57BL/6 and TLR3KO mice were evaluated by flow cytometry to determine binding specificity. mAb 5429 was not used in this assay since the mouse Fc region of this chimeric antibody was expected to contribute to non-specific binding. mAb c1811 exhibited no binding to TLR3KO macrophages, and increased binding to the cell surfaces of C57BL/6 peritoneal macrophages,

suggesting a specificity of the mAb for TLR3 (Figure 10). mAb 5429, having the same binding regions as mAb c1811, is assumed to have the same binding specificity as mAb c1811.

Example 9

TLR3 antibody antagonists protect from TLR3-mediated systemic inflammation

Model

[0171] The Poly(I:C)-induced systemic cytokine/chemokine model was used as a model of TLR3-mediated systemic inflammation. In this model, poly(I:C) (PIC) delivered intraperitoneally induced a systemic cytokine and chemokine response that was partially TLR3-mediated.

[0172] Female C57BL/6 mice (8-10 weeks old) or female TLR3KO mice (C57BL/6 background; 8-10 weeks old, Ace Animals, Inc.) were given mAb 5429 at 10, 20 or 50 mg/kg in 0.5 ml PBS, mAb c1811 at 2, 10 or 20 mg/kg in 0.5 ml PBS or 0.5 ml PBS alone (vehicle control) subcutaneously. 24 hours after antibody dosing, mice were given 50 µg poly(I:C) (Amersham Cat. No. 26-4732 Lot no. IH0156) in 0.1 ml PBS intraperitoneally. Retro-orbital blood was collected 1 and 4 hours after the poly(I:C) challenge. Serum was prepared from whole blood and analyzed for cytokine and chemokine concentrations by Luminex.

Results

[0173] Poly(I:C) delivered intraperitoneally induced a systemic cytokine and chemokine response that was partially TLR3-mediated, as evidenced by the significantly reduced production of a panel of chemokines and cytokines in the TLR3KO animals (Table 9A). The TLR3-dependent poly(I:C)-induced mediators were IL-6, KC, CCL2/MCP-1 and TNF-α at 1 hr post-poly(I:C) challenge, and IL-1α, CCL5/RANTES and TNF-α at 4 hr post-poly(I:C) challenge. Both mAb c1811 and mAb 5429 significantly reduced levels of these TLR3-dependent mediators, demonstrating the ability of the antibodies to reduce TLR3 signaling *in vivo* (Table 9B). Values in Table 9 are shown as mean cytokine or chemokine concentrations in pg/ml of six animals/group ±SEM. These data suggest that TLR3 antagonism can be beneficial in reducing excess TLR3-mediated cytokine and chemokine levels in conditions such as cytokine storm or lethal shock.

Table 9A.

	C57BL/6		TLR3KO	
PIC	-	+	-	+
mAb 5429 (mg/kg)	-	-	-	-
mAb c1811 (mg/kg)	-	-	-	-
1 h PIC challenge				
TNFα	6.005 ± 0.32	319.4 ± 34.1 *	9.13 ± 4.41	43.80 ± 10.13**
KC	129.3 ± 9.83	2357 ± 491.5*	152.0 ± 21.34	432.3 ± 90.66**
IL-6	40.91 ± 5.66	5317 ± 856.7*	120.1 ± 99.99	1214 ± 294.9**
MCP-1	84.67 ± 18.45	694.6 ± 127.8*	67.85 ± 34.16	249.9 ± 55.60**
4 h PIC challenge				
IL-1α	28.21 ± 17.78	796.7 ± 45.0*	13.94 ± 13.84	408.5 ± 29.91**
RANTES	20.87 ± 1.738	4511 ± 783.4*	36.01 ± 4.484	706.3 ± 84.36**
TNFα	0.10 ± 0	561.7 ± 81.84*	3.215 ± 3.115	305.8 ± 53.63**
*p<0.001: One Way ANOVA to C57BL/6 PBS				
**p<0.001 One Way ANOVA to C57BL/6 PIC				

Table 9B.

C57BL/6						
PIC	+	+	+	+	+	+
mAb 5429 (mg/kg)	50	20	10	-	-	-
mAb c1811 (mg/kg)	-	-	-	20	10	2
1 h PIC challenge						
TNF- α	29.33 $\pm$ 3.78***	31.05 $\pm$ 1.59***	59.55 $\pm$ 12.71 "	32.54 $\pm$ 3.89***	42.22 $\pm$ 7.04***	42.61 $\pm$ 10.58***
KC	466.3 $\pm$ 92.35***	440.3 $\pm$ 10.01***	744.6 $\pm$ 103.1**	637.3 $\pm$ 151.0***	944.2 $\pm$ 130.9**	919.3 $\pm$ 231.2**
IL-6	480.2 $\pm$ 62.88***	375.9 $\pm$ 46.14***	705.2 $\pm$ 149.8***	739.2 $\pm$ 113.3***	1047 $\pm$ 222***	1229 $\pm$ 378.4***
MCP-1	168.5 $\pm$ 15.04**	321.6 $\pm$ 206.7	219.2 $\pm$ 70.58*	184.0 $\pm$ 14.92**	278.3 $\pm$ 53.57	414.9 $\pm$ 97.17
4 h PIC challenge						
IL-1 α	343.0 $\pm$ 33.01***	452.6 $\pm$ 94.86**	481.1 $\pm$ 121.0*	354.8 $\pm$ 45.43***	351.7 $\pm$ 68.85***	352.4 $\pm$ 39.60***
RANTES	1381 $\pm$ 169.7***	2439 $\pm$ 308.7**	1601 $\pm$ 398.9***	1303 $\pm$ 168.0***	1365 $\pm$ 474.1***	2209 $\pm$ 402.5**
TNF- α	100.1 $\pm$ 8.5***	205.1 $\pm$ 41.85***	226.1 $\pm$ 64.72***	138.9 $\pm$ 26.0***	121.6 $\pm$ 38.85***	223.8 $\pm$ 47.74***
***p<0.001, **p<0.01, *p<0.05: One Way ANOVA statistics were compared to the C57BL/6 + PIC group						

Example 10**TLR3 antibody antagonists reduce airway hyperresponsiveness**Model

[0174] Airway hyperresponsiveness was induced by Poly(I:C).

[0175] Female C57BL/6 mice (12 weeks old) or female TLR3KO mice (C57BL/6 background; 12 weeks old, Ace Animals, Inc.) were anesthetized with isoflurane and several doses (10-100 μ g) of poly(I:C) in 50 μ l sterile PBS were administered intranasally. Mice received three administrations of poly(I:C)(or PBS) with a 24 hour rest period between each administration. 24 hours following the last poly(I:C)(or PBS) administration, lung function and airway hyperresponsiveness to methacholine were measured using whole body plethysmography (BUXCO system). The mice were placed into the whole body plethysmograph chamber and allowed to acclimate for at least 5 minutes. Following baseline readings, mice were exposed to increasing doses of nebulized methacholine (Sigma, St. Louis, MO). The nebulized methacholine was administered for 2 minutes, followed by a 5-minute data collection period, followed by a 10-minute rest period before subsequent increasing-dose methacholine challenges. The increased airflow resistance was measured as Enhanced Pause (Penh) and is represented as the average Penh value over the 5-minute recording period (BUXCO system). Following lung function measurements, mice were euthanized and the lungs were cannulated. Bronchoalveolar lavages (BAL) were performed by injecting 1 ml of PBS into the lungs and retrieving the effluent. The lung tissues were removed and frozen. BAL fluids were centrifuged (1200 rpm, 10 min.) and the cell-free supernatants were collected and stored at -80°C until analysis. Cell pellets were resuspended in 200 μ l PBS for total and differential cell counts. The multiplex assay was performed following the manufacturer's protocol and the Multiplex Immunoassay Kit (Millipore, Billerica, MA).

Results

[0176] Previous observations demonstrated that the intranasal administration of poly(I:C) induced a TLR3-mediated impairment in lung function in mice with increased enhanced pause (PenH) measurement in whole body plethysmography (Buxco) at baseline and an increased responsiveness to aerosolized methacholine (an indicator of airway hyperresponsiveness) (PCT Publ. No. WO06/060513A2). This impairment in the lung function was associated with neutrophil recruitment into the lung, and increased levels of pro-inflammatory cytokines/chemokines in the lung. In this study, the effect of mAb 1811 and mAb 5429 was evaluated in poly(I:C)-induced impairment in lung function by administering each antibody at 50 mg/kg subcutaneously prior to poly(I:C) challenge.

[0177] TLR3-mediated impairment of lung function was significantly reduced by treatment of animals with TLR3 antibody antagonists prior to the poly(I:C) challenge. TLR3-mediated increases in baseline PenH and airway sensitivity to methacholine were prevented in the anti-TLR3 antibody-treated animals (Figure 11). Further, TLR3-mediated recruitment of neutrophils into the mouse lung and generation of chemokines in the airways were reduced in the anti-TLR3 antibody-treated animals. The neutrophil numbers (Figure 12) and the CXCL10/IP-10 levels (Figure 13) were measured from the collected bronchoalveolar lavage fluid (BALF). The studies were repeated at least three times with similar results. Data shown in Figures 11, 12 and 13 are from one representative study. Each symbol represents a data point from one mouse, and the horizontal bars show group means. The study demonstrated that systemically-administered TLR3 antibody antagonists reached the lung, reduced TLR3-mediated impairment of lung function, neutrophil infiltration into the airway, chemokine generation and respiratory tract inflammation in the used model. Thus, TLR3 antagonists may be beneficial in the treatment or prevention of respiratory diseases characterized by airway hyperresponsiveness, such as asthma, allergic rhinitis, chronic obstructive pulmonary disease (COPD), and cystic fibrosis.

Example 11

TLR3 antibody antagonists protect from inflammatory bowel disease

Model

[0178] The DSS colitis Model was used as a model of inflammatory bowel disease.

[0179] Female C57BL/6 mice (<8 weeks old) or female TLR3KO mice (C57BL/6 background; <8 weeks old weighing between 16.5g and 18g, Ace Animals, Inc.) were fed gamma-irradiated food starting on day -1. DSS (Dextran sulfate) (MP Biomedicals, Aurora, OH, Catalog no: 160110; 35-50kDa; 18-20% Sulfur, Lot no. 8247J) was diluted in autoclaved acidified drinking water to a final concentration of 5%. The DSS-water was administered for 5 days, after which it was replaced with plain water. Mice were allowed to drink water ad libitum throughout the study. All water bottles were weighed every day to record water consumption. On days 0, 2, and 4 mice were dosed intraperitoneally with 5 mg/kg (0.1 mg in 0.1 ml PBS) mAb 5429, mouse anti-TNF- α antibody, or PBS as a control. Mice were monitored daily throughout the study and were weighed on days 0 through 4 and day 7. Mice were euthanized on days 2 and 7 of the study. Abdominal cavities were opened and the ascending colons cut where they join the cecum. Colons were collected and fixed in 10% neutral buffered formalin. Colons were paraffin-embedded, sectioned and H&E stained (Qualtek Molecular Labs, Santa Barbara, CA). Colonic histopathological assessments were done in a blinded fashion by a veterinary pathologist as described below (PathoMetrix, San Jose, CA).

Histopathologic evaluation

[0180] Two segments of large intestine, colon and rectum were evaluated and scored for the following changes: (i) single cell necrosis; (ii) epithelial ulceration; (iii) epithelial sloughing; (iv) cryptal abscess; (v) cell proliferation; (vi) cryptal cell proliferation; (vii) granulation tissue formation in the lamina propria; (viii) granulation tissue in the submucosa; (ix) submucosal inflammatory cell infiltrate, neutrophil predominant; and (x) submucosal edema.

[0181] A single, overall score of severity was given based on the following standards:

- 0 - non-existent
- 1 - mild, focal or occasionally found
- 2 - mild, multifocal
- 3 - moderate, frequently found but in limited areas
- 4 - severe, frequently found in many areas or extensions

of the tissue submitted

5 - very severe, extends to large portions of the tissue

submitted

Results

[0182] Previous observations demonstrated that TLR3KO animals showed significantly reduced histopathology compared with wild type mice in a model of inflammatory bowel disease induced by DSS ingestion (PCT Publ. No. WO06/60513A2), thus suggesting that TLR3 signaling plays a role in the pathogenesis in this model. It has been reported that commensal bacterial RNA or mammalian RNA released from necrotic cells can act as endogenous ligands to stimulate TLR3 signaling (Kariko et al., Immunity 23165-231175 2005; Kariko et al., J. Biol. Chem. 279:12542-12550 2004), and therefore TLR3 stimulation by endogenous ligands in the gut may enhance and perpetuate inflammation in the DSS colitis model.

[0183] Disease severity was ameliorated in DSS-exposed animals upon treatment with anti-TLR3 antibodies, as assessed by compound histopathology scores (Figure 14). Figure 14 shows means, standard deviations and 95% confidence intervals for disease severity scores as horizontal bars. Significant reduction in the scores were observed in the wild type DSS-exposed animals treated with anti-TLR3 antibodies ($p < 0.05$) when compared to untreated wild type animals. DSS-exposed TLR3KO animals were protected from DSS-induced changes. DSS-exposed animals receiving anti-mouse TNF- α mAb demonstrated no improvement in histopathology in the DSS model. Therefore, the DSS model may be useful in evaluating therapeutics that may target the human patient population that is non-responsive to anti-TNF- α therapies, and neutralizing anti-TLR3 antibodies may have the potential to provide benefit to patients with inflammatory bowel disease who do not respond to anti-TNF- α therapies.

Model

[0184] The T cell Transfer Model was used as a model of inflammatory bowel disease. In this model, gut inflammation was induced in SCID mice by the transfer of a population of regulatory T cell-devoid naive T cells from immune-competent mice, which attack antigen-presenting cells in the gut mucosa.

[0185] Naive T-cells (CD4+CD45RB^{high} T cells) were injected intraperitoneally into SCID recipients to induce chronic colitis. Mice were given either PBS (500 μ l/mouse intraperitoneally; vehicle control), mAb 5429 (0.1 mg/mouse intraperitoneally), or anti-TNF- α antibody (0.05 mg/mouse intraperitoneally; positive control) beginning 48 hours following transfer of T-cells and then twice weekly throughout the 8 week study. At 8 weeks following T-cell transfer (or when mice lost >15% of their original body weight) animals were euthanized and colons removed. Colons were fixed, paraffin-embedded and H&E stained. Histopathology (cell infiltration, crypt abscesses, epithelial erosion, goblet cell loss, and bowel wall thickening) was assessed quantitatively in a blinded fashion.

Results

[0186] Disease severity was ameliorated in animals that received T-cell transfer upon treatment with anti-TLR3 antibodies, as assessed by significant reduction in the histopathology sum of scores when compared to the control animals ($p < 0.05$) (Figure 15A). For the sum of scores, crypt abscesses, ulceration, neutrophil influx, goblet cell loss, abnormal crypts, lamina propria inflammation and transmural involvement was assessed. Significant reduction was observed with crypt abscesses, ulceration and neutrophil influx (for all $p < 0.05$) (Figure 15B). Anti-TNF- α antibody was used as a positive control at doses known to provide optimal benefit.

[0187] Studies using two well known models of inflammatory bowel diseases, the DSS and the T-cell transfer model, demonstrated that systemically delivered TLR3 antibody antagonists reached the gut mucosa and reduced gastrointestinal tract inflammation induced through two different pathogenic mechanisms. Thus, TLR3 antagonists may be beneficial for the treatment of inflammatory bowel diseases, including anti-TNF- α -refractory cases, and other immune-mediated pathologies in the gastrointestinal tract.

Example 12

TLR3 antibody antagonists protect from collagen-induced arthritis

Model

[0188] The collagen-induced arthritis (CIA) model was used as a model of rheumatoid arthritis.

[0189] Male B10RIII mice (6-8 weeks old, Jackson Labs) were divided into groups of 15 per group (arthritis groups)

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or 4 per group (control mice). Arthritis groups were anesthetized with Isoflurane and given injections of Type II collagen (Elastin Products) and Freund's complete adjuvant supplemented with *M. tuberculosis* (Difco) on days 0 and 15. On day 12, mice with developing type II collagen arthritis were randomized by body weight into treatment groups and were dosed subcutaneously (SC) on days 12, 17, and 22 (d12, d17, 2d2) with mAb 5429 (25 mg/kg), the negative control antibody CVAM (a recombinant mAb of no known specificity in the mouse) (5 mg/kg) or anti-TNF- α antibody (5 mg/kg, positive control). In addition, control groups of mice were treated with vehicle (PBS) or dexamethasone (0.5 mg/kg, Dex, reference compound) subcutaneously (SC) daily (QD) on days 12-25. Animals were observed daily from days 12 through 26. Fore and Hind paws were evaluated by a clinical scoring system (shown below). Animals were euthanized on study day 26 and histopathology was assessed in a blinded fashion (scoring system described below). Efficacy evaluation was based on animal body weights, and clinical arthritis scores. All animals survived to study termination.

Clinical scoring criteria for fore and hind paws

[0190]

- 0 - normal
- 1 - hind or fore paw joint affected or minimal diffuse erythema and swelling
- 2 - hind or fore paw joints affected or mild diffuse erythema and swelling
- 3 - hind or fore paw joints affected or moderate diffuse erythema and swelling
- 4 - marked diffuse erythema and swelling, or =4 digit joints affected)
- 5 - severe diffuse erythema and severe swelling entire paw, unable to flex digits)

Histopathologic scoring methods for mouse joints with Type II collagen arthritis

[0191] When scoring paws or ankles from mice with lesions of type II collagen arthritis, severity of changes as well as number of individual joints affected were considered. When only 1-3 joints of the paws or ankles out of a possibility of numerous metacarpal/metatarsal/digit or tarsal/tibiotarsal joints were affected, an arbitrary assignment of a maximum score of 1, 2 or 3 for parameters below was given depending on severity of changes. If more than 2 joints were involved, the criteria below were applied to the most severely affected/majority of joints.

[0192] Clinical data for paw scores were analyzed using AUC for days 1-15, and % inhibition from controls were calculated.

Inflammation

[0193]

- 0 - normal
- 1 - minimal infiltration of inflammatory cells in synovium and periarticular tissue of affected joints
- 2 - mild infiltration, if paws, restricted to affected joints
- 3 - moderate infiltration with moderate edema, if paws, restricted to affected joints
- 4 - marked infiltration affecting most areas with marked edema
- 5 - severe diffuse infiltration with severe edema

Pannus

[0194]

- 0 - normal
- 1 - minimal infiltration of pannus in cartilage and subchondral bone
- 2 - mild infiltration with marginal zone destruction of hard tissue in affected joints
- 3 - moderate infiltration with moderate hard tissue destruction in affected joints
- 4 - marked infiltration with marked destruction of joint architecture, most joints
- 5 - severe infiltration associated with total or near total destruction of joint architecture, affects all joints

Cartilage Damage

[0195]

0 - normal

1 - minimal to mild loss of toluidine blue staining with no obvious chondrocyte loss or collagen disruption in affected joints

2 - mild loss of toluidine blue staining with focal mild (superficial) chondrocyte loss and/or collagen disruption in affected joints

3 - moderate loss of toluidine blue staining with multifocal moderate (depth to middle zone) chondrocyte loss and/or collagen disruption in affected joints

4 - marked loss of toluidine blue staining with multifocal marked (depth to deep zone) chondrocyte loss and/or collagen disruption in most joints

5 - severe diffuse loss of toluidine blue staining with multifocal severe (depth to tide mark) chondrocyte loss and/or collagen disruption in all joints

Bone Resorption

[0196]

0 - normal

1 - minimal with small areas of resorption, not readily apparent on low magnification, rare osteoclasts in affected joints

2 - mild with more numerous areas of, not readily apparent on low magnification, osteoclasts more numerous in affected joints

3 - moderate with obvious resorption of medullary trabecular and cortical bone without full thickness defects in cortex, loss of some medullary trabeculae, lesion apparent on low magnification, osteoclasts more numerous in affected joints

4 - marked with full thickness defects in cortical bone, often with distortion of profile of remaining cortical surface, marked loss of medullary bone, numerous osteoclasts, affects most joints

5 - severe with full thickness defects in cortical bone and destruction of joint architecture of all joints

Results

[0197] Dexamethasone (Dex) and anti-mouse TNF- α antibody was used as a positive control, PBS was used as vehicle control, and CVAM was used as a negative control antibody. All treatments were initiated on day 12 of the study, during the development of joint disease. Disease incidence for vehicle-treated disease control animals was 100% by study day 22. Negative control groups treated with vehicle or CVAM antibody had the highest clinical scores. Significantly reduced clinical scores were observed for the groups treated with Dex ($p < 0.05$ for d18-d26), 5 mg/kg anti-TNF- α antibody ($p < 0.05$ for d18-26), or 25 mg/kg mAb 5429 ($p < 0.05$ for d18-d23 and d25-d26) (Figure 16). Clinical arthritis scores expressed as area under the curve (AUC) were significantly reduced by treatment with 25 mg/kg mAb 5429 (43% reduction), 5 mg/kg anti-TNF- α antibody (52%), or Dex (69%) as compared to vehicle controls. Figure 17 shows means and standard deviations for AUC for each group.

[0198] Histopathological effects of the treatments were also assessed. Paw bone resorption was significantly decreased by treatment with 25 mg/kg mAb 5429 (47% decrease) as compared to vehicle controls. Positive control mice treated with 5 mg/kg anti-TNF- α antibody had significantly decreased paw inflammation (33%), cartilage damage (38%), and summed paw scores (37%). Treatment with Dex significantly reduced all paw histopathology parameters (73% reduction of summed scores).

[0199] These data demonstrate that TLR3 antibody antagonists improve clinical and histopathological disease symptoms in the CIA model, and suggest the use of TLR3 antagonists for treatment of rheumatoid arthritis.

Example 14

TLR3 antibody antagonists protect from acute lethal viral infections

Model

[0200] An influenza A virus challenge model was used as a model of acute lethal viral infection.

[0201] On Day -1, 4, 8, and 12, female C57BL/6 mice (12 weeks old) or female TLR3KO mice (C57BL/6 background; 12 weeks old, ACE Animals, inc., 15 mice per group) were dosed subcutaneously 20 mg/kg mAb 5429, or PBS alone. On day 0, the mice were anesthetized by isoflurane and were intranasally administered Influenza A/PR/8/34 virus (ATCC, Rockland, MD, Lot no. 218171), in 25 μ l PBS (equivalent to $10^{5.55}$ CEID₅₀). Animals were observed two times a day for changes in body weight and survival over the period of 14 days. A clinical scoring system was used to evaluate the

level of disease progression and subtle improvements in response to Influenza A virus treatment.

Clinical scores

[0202]

- 0 - normal, alert and reactive, no visible signs of illness
- 1 - ruffled coat, with or without slightly reduced ambulation
- 2 - ruffled coat, hunched posture when walking, reluctant ambulation, labored breathing
- 3 - ruffled coat, labored breathing, ataxia, tremor
- 4 - ruffled coat, inability to ambulate with gentle prodding, unconsciousness, feels cold to the touch
- 5 - found dead

Results

[0203] Survival, daily clinical scores, and changes in body weight were evaluated in the study. Both influenza A infected WT mice administered mAb 5429 (20 mg/kg) and influenza A infected TLR3KO not receiving mAb 5429 demonstrated a statistically significant increase in survival ($p < 0.001$ and $p < 0.01$, respectively) when compared to C57BL/6 mice inoculated with the Influenza virus, indicating that antagonism or deficiency of TLR3 can prevent influenza - induced mortality (Figure 18). Clinical scores were significantly reduced in the group receiving 20 mg/kg mAb 5429, as well as in the TLR3KO group (Figure 19). The body weight of the mice was observed over a period of 14 days after influenza virus administration. Body weight decreased steadily in C57BL/6 mice dosed with Influenza A virus. However, both the C57BL/6 mice dosed with 20 mg/kg mAb 5429 and the TLR3KO mice demonstrated significantly greater body weight relative to the WT C57BL/6 mice inoculated with Influenza virus (Figure 20). These results demonstrated that TLR3 antibody antagonists reduced clinical symptoms and mortality in an acute lethal influenza viral infection model, and suggested that TLR3 antagonists may provide protection for humans in acute infectious states.

Example 15

TLR3 antibody antagonists improve hyperglycemia and reduce plasma insulin

Model

[0204] The Diet-induced obesity (DIO) model was used as a model of hyperglycemia and insulin resistance, and obesity.

[0205] C57BL/6 WT animals (about 3 weeks old, Jackson Labs) and TLR3KO animals (C57BL/6 background; about 3 weeks old, Ace Animals, Inc.) were maintained on a high fat diet for 12 to 16 weeks. Both TLR3KO and WT C57BL/6 mice were fed either with normal chow or high-fat diet (Purina TestDiet cat. no. 58126) consisting of 60.9% kcal fat and 20.8% kcal carbohydrates. Mice were maintained on a 12:12-h light-dark cycle, with water and food ad libitum. The weight of each mouse within each group was measured weekly. mAb 5429 was given intraperitoneally twice a week for the first week followed by once a week dosing for total of 7 weeks. Fasting retro-orbital blood serum samples were used for insulin measurements at the time points indicated. Glucose tolerance tests were performed by i.p administration of glucose at 1.0 mg/g body weight after overnight fast at week 7. In addition, fasting insulin and glucose levels were measured.

[0206] HOMA-IR was determined from the equation based on the levels of fasting glucose and insulin levels (12) using following equation: $\text{HOMA-IR} = ((\text{fasting glucose (mmol/l)} \times \text{fasting insulin (mU/l)}) / 22.5)$ (Wallace et al., Diabetes Care 27:1487-1495, 2004). Fasting blood glucose (BG) was determined using glucose oxidase assay. Fasting insulin levels were determined using the insulin rat/mouse ELISA kit (Crystal Chem, cat. No. 90060).

Results

[0207] After 12-16 weeks on high fat diet, the WT DIO animals were hyperglycemic and hyperinsulinemic. Glucose tolerance was improved in the WT DIO animals but not in the TLR3KO DIO animals upon treatment with mAb 5429. Significantly reduced blood glucose levels were observed in mAb 5429 treated animals post glucose challenge at 60, 90, 120, and 180 min when compared to control (PBS only) (Figure 21A). About 21% reduction in AUC was observed in the mAb 5429 treated WT DIO animals when compared to the WT DIO mice not receiving the mAb. Fasting insulin levels were also reduced in the WT DIO animals treated with mAb 5429 (Figure 22). TLR3KO DIO animals showed no improvement in fasting insulin upon mAb 5429 treatment. Homeostatic model assessment (HOMA) analysis indicated improved insulin sensitivity in the WT DIO animals treated with mAb 5429, but not in the TLR3KO DIO animals. The

HOMA-IR values were 14.0 ± 9.8 , 8.7 ± 4.9 , 9.0 ± 3.0 for WT DIO, 5 mg/kg of WT DIO mAb 5429, and 20 mg/kg of WT DIO mAb 5429 animals, respectively. No effect was observed in TLR3KO DIO animals.

[0208] The study demonstrated that TLR3 antibody antagonists improved insulin resistance and reduced fasting glucose in the DIO model without weight loss, suggesting that TLR3 antagonists may be beneficial for the treatment of hyperglycemia, insulin resistance, and type II diabetes.

Example 16

TLR3 antibody antagonists protect from bacteria and virus-induced inflammatory responses

Reagents

[0209] Nontypeable *Haemophilus influenza* (NTHi) strains 35, isolated from a COPD patient with bacterial exacerbations, was obtained from Dr. T. F. Murphy (Buffalo VA Medical Center, Buffalo, NY). Human rhinovirus 16 was obtained from the American Type Culture Collection (ATCC) with TCID₅₀= 2.8×10^7 /ml.

NTHi stimulation assays

[0210] NHBE cells (Lonza, Walkersville, MD) were seeded in Microtest 96-well tissue culture plates (BD Biosciences, Bedford, MA) at 1×10^5 /well. NTHi grown on agar plates for 16-20 hr were resuspended in growth medium at $\sim 2 \times 10^8$ cfu/ml, treated with 100 μ g/ml gentamycin for 30 min. and added at $\sim 2 \times 10^7$ /well to 96-well plates containing NHBEs. After 3 hours, supernatants were removed and replaced with fresh growth medium with or without antibodies (0.08 to 50 μ g/ml final concentration). After additional 24 hr incubation, presence of cytokines and chemokines in cell supernatants was assayed in triplicate with a Cytokine 25-plex AB bead kit, Human (including IL-1 β , IL-1RA, IL-2, IL-2R, IL-4, IL-5, IL-6, IL-7, IL-8, IL-10, IL12p40p70, IL-13, IL-15, IL-17, TNF- α , IFN- α , IFN- γ , GM-CSF, MIP-1 α , MIP-1 β , IP-10, MIG, Eotaxin, RANTES and MCP-1) (Life Technologies, Carlsbad, CA) in the Luminex 100IS multiplex fluorescence analyzer and reader system (Luminex Corporation, Austin, TX).

Rhinovirus stimulation assays

[0211] NHBE cells were seeded in Microtest 96-well tissue culture plates (BD Biosciences, Bedford, MA) at 1×10^5 cells/well. The next day, antibodies (0.08 to 50 μ g/ml final concentration) were added to NHBE or BEAS-2B cells and incubated for 1 hr, followed by addition of 10 μ l/well of rhinovirus. After additional 24 hr incubation, presence of cytokines and chemokines in cell supernatants was assayed by luminex assays as described above.

Results

[0212] mAb 15EVQ inhibited NTHi induced IP-10/CXCL10 and RANTES/CCL5 production in a dose-dependent manner, while the control antibody, human IgG4 (Sigma, St. Louis, MO), showed no inhibitory effect on NTHi stimulation (Figure 23A). mAb 15EVQ also inhibited rhinovirus induced CXCL10/IP-10 and CCL5/RANTES production (Figure 23B).

Example 17

TLR3 antibody antagonists suppress inflammatory responses in astrocytes

Methods

[0213] Normal human astrocytes from 2 donors (Lonza, Walkersville, MD) were plated in a 24 well plate at 75,000 cells/well and allowed to attach overnight. The next day, the astrocytes were treated with 200 ng/ml poly(I:C) and/or 10 μ g/ml mAb 18 for 24 hours. Cytokines were measured by Luminex.

Results

[0214] Poly(I:C)- induced production of IL-6, IL-8, IL-12, IFN- α , IFN- γ , CXCL9/MIG, CCL3/MIP-1a, CCL4, CCL5/RANTES and CXCL10/IP-10 were inhibited by mAb 18, as shown in Table 10.

Table 10.

Donor 1	IL-6	IL-8	IL-12	IFN- α	IFN- γ
untreated	876.0 $\pm$ 36.8	539.7 $\pm$ 32.6	16.6 $\pm$ 0.5	28.8 $\pm$ 1.5	12.3 $\pm$ 0.3
mAb 18	1011.9 $\pm$ 57.4	1401.9 $\pm$ 49.7	17.1 $\pm$ 0.5	31.6 $\pm$ 0.7	10.4 $\pm$ 0.2
Poly(I:C)	ol*	ol	30.3 $\pm$ 1.5	47.1 $\pm$ 3.1	35.9 $\pm$ 1.0
Poly(I:C) + mAb 18	2225.0 $\pm$ 108.1	6104.4 $\pm$ 259.9	16.8 $\pm$ 0.9	30.5 $\pm$ 1.6	11.7 $\pm$ 0.6
Donor 2					
untreated	729.1 $\pm$ 7.1	248.2 $\pm$ 4.7	14 $\pm$ 0.5	19.5 $\pm$ 1.8	10.5 $\pm$ 0.5
mAb 18	779.0 $\pm$ 9.8	1132.6 $\pm$ 30.6	14.3 $\pm$ 0.6	20.8 $\pm$ 1.9	10.5 $\pm$ 0.1
Poly(I:C)	ol	ol	25.5 $\pm$ 0.4	36.3 $\pm$ 1.9	30.8 $\pm$ 0.9
Poly(I:C) + mAb 18	3393.3 $\pm$ 107.5	8660.4 $\pm$ 354.3	16.2 $\pm$ 0.3	24.7 $\pm$ 1.2	12.6 $\pm$ 0.3
Donor 1	CXCL9/MIG	CCL3/MIP-1a	CCL4	CCL5/RANTES	CXCL10/IP-10
untreated	12.6 $\pm$ 0.7	21 $\pm$ 0.9	14.8 $\pm$ 0.7	bl**	bl
mAb 18	14.8 $\pm$ 1.7	19.5 $\pm$ 1.5	14.8 $\pm$ 1.1	bl	bl
Poly(I:C)	78.3 $\pm$ 4.8	1569.3 $\pm$ 36.9	159.7 $\pm$ 12.7	788.2 $\pm$ 94.9	461.4 $\pm$ 10.3
Poly(I:C) + mAb 18	18.5 $\pm$ 1.6	31.2 $\pm$ 1.9	13.2 $\pm$ 0.9	bl	6.9 $\pm$ 0.5
Donor 2					
untreated	9.9 $\pm$ 1.6	12.3 $\pm$ 1.7	11.3 $\pm$ 0.3	bl	bl
mAb 18	8.9 $\pm$ 0.7	13.2 $\pm$ 1.5	11.1 $\pm$ 0.7	bl	bl
Poly(I:C)	62 $\pm$ 3.8	1552.9 $\pm$ 41.1	140.7 $\pm$ 4.8	546.8 $\pm$ 21.7	533.2 $\pm$ 15
Poly(I:C) + mAb 18	18.3 $\pm$ 2.7	66.6 $\pm$ 3.8	12.1 $\pm$ 0.8	bl	29.1 $\pm$ 6.2
	*ol: over detection level				
	**bl: below detection level				

Example 18**TLR3 antibody antagonists suppress inflammatory responses in endothelial cells**Methods

[0215] HUVEC cells (Lonza, Walkersville, MD) were cultured in serum-containing growth medium recommended by Lonza. Cells were resuspended in serum-free media (Lonza, Walkersville, MD), plated in 96-well plates at 3×10^5 cells/ml, and incubated at 37°C, 5%CO₂ for 24 hrs. Poly(I:C) (GE Healthcare, Piscataway, NJ) was added at increasing concentrations (1.5 to 100 μ g/ml) and incubated for another 24 hours at 37°C. For cytokine inhibition assays, mAb 15EVQ was added to the cells at various concentrations (0 - 50 μ g/ml) and incubated for 30 min, after which 20 μ g/ml poly(I:C) was added for 24 hours. Cell supernatants were collected and cytokine levels were measured using the human cytokine 30-plex kit and Luminex MAP technology (Invitrogen Corp., Carlsbad, CA). To measure sICAM-1 expression, the HUVEC cells were treated with 20 μ g/ml poly(I:C) and various concentrations of mAb 15EVQ (0.8 - 50 μ g/ml). The cell supernatants were analyzed for sICAM-1 expression by ELISA (R&D systems). Cell viability was measured using the CellTiterGlo kit (Promega, Madison, WI).

Results

[0216] HUVEC cells produced the following cytokines in response to poly(I:C): IL-1RA, IL-2, IL-2R, IL-6, IL-7, CXCL8/IL-8, IL-12 (p40/p70), IL-15, IL-17, TNF- α , IFN- α , IFN- γ , GM-CSF, CCL3/MIP-1 α , CCL4/MIP-1 β , CXCL10/IP-10, CCL5/RANTES, CCL2/MCP-1, VEGF, G-CSF, FGF-basic, and HGF (Table 11). mAb 15EVQ dose-dependently reduced levels of all cytokines induced by poly(I:C) (Table 12). The ability of mAb 15EVQ to reduce poly(I:C)-induced production of TNF- α , CCL2/MCP-1, CCL5/RANTES, and CXCL10/IP-10 suggested that inhibition of TLR3-mediated activities may

protect against leukocyte and T cell infiltration that can lead to atherosclerosis. Also, inhibition of VEGF by mAb 15EVQ suggested a potential benefit of TLR3 blockade in pathologies mediated by VEGF including angiogenesis in a variety of cancers and ocular diseases such as age-related macular degeneration.

[0217] TNF- α and IFN- γ function in leukocyte recruitment and increase the expression of adhesion molecules on the activated endothelium (Doukas et al., Am. J. Pathol. 145:137-47, 1994; Pober et al., Am. J. Pathol. 133:426-33, 1988). CCL2/MCP-1, CCL5/RANTES, and CXCL10/IP-10 have been implicated in monocyte and T cell recruitment and contribute to the development of atherosclerosis (Lundberg et al., Clin. Immunol. 2009). The generation of VEGF by endothelial cells has been linked to abnormal tissue growth or tumors in a variety of cancers during angiogenesis (Livengood et al., Cell. Immunol. 249:55-62, 2007).

[0218] Soluble Intercellular Adhesion Molecule 1 (sICAM-1) is generated by proteolytic cleavage and is a marker for endothelial cell activation. ICAM-1 plays a key role in leukocyte migration and activation and is upregulated on endothelial cells and epithelial cells during inflammation where it mediates adhesion to leukocytes via integrin molecules LFA-1 and Mac-1. Poly(I:C)

activated the endothelial cells to upregulate sICAM-1 expression and the upregulation was reduced by treatment with mAb 15EVQ (Figure 24A).

Table 11.

Poly(I:C) μ g/ml	IL-6	CXCLB/IL-8	CCL2/MCP-1
10	848.8 + 50.9	12876.0 + 2314.0	11813.4 + 1420.9
5	751.3 + 2.1	11363.7 + 108.2	11365.7 + 113.1
2.5	607.1 + 91.6	10961.5 + 2200.7	11607.3 + 2155.7
1.25	419.2 + 178.4	9631.5 + 3675.8	11690.9 + 3189.9
0.63	263.8 + 81.4	6231.9 + 1568.0	9075.6 + 1152.2
0.31	183.5 + 168.3	5257.9 + 1855.0	8106.8 + 1193.1
0.16	111.9 + 72.5	4057.6 + 1127.4	6619.8 + 1728.2
no poly(I:C)	0.00	1286.6 + 300.8	1360.1 + 245.4
Poly(I:C) μ g/ml	IL-2R	IL-15	IL-17
100	784.4 + 45.4	61.3 + 12.5	43.8 + 5.3
50	718.6 + 56.8	61.3 + 12.5	47.6 + 0
25	735.7 + 23.4	56.7 + 18.9	58.3 + 4.9
12.5	650.5 + 29.8	38.8 + 6.5	39.8 + 10.9
6.25	643.4 + 39.9	34.2 + 0	32.1 + 0
3.13	681.8 + 24.3	38.8 + 6.5	43.8 + 5.3
1.56	578.6 + 10.5	29.4 + 6.7	36.1 + 5.6
no poly(I:C)	0.0	0.0	0.0
Poly(I:C) μ g/ml	IFN α	CXCL10/IP-10	CCL4/MP-1 β
100	50.7 + 0	3803.1 + 185.5	234.5 + 19.7
50	44.9 + 1.7	2235.9 + 184.6	291.6 + 41.8
25	46.1 + 0	2403.0 + 271.9	278.7 + 4.7
12.5	41.2 + 3.5	2185.4 + 64.9	243.8 + 63.4
6.25	36.1 + 0	2100.0 + 288.1	201.9 + 46.2
3.13	40.0 + 1.8	3553.2 + 197.1	191.5 + 20.8
1.56	42.5 + 1.7	2064.3 + 242.1	165.3 + 16.3

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(continued)

Poly(I:C) $\mu\text{g/ml}$	IFN α	CXCL10/IP-10	CCL4/MP-1 β
no poly(I:C)	0.0	0.0	0.0
Poly(I:C) $\mu\text{g/ml}$	RANTES	TNF α	VEGF
100	6266.9 + 1708.7	12.8 + 3.2	581.1 + 181.4
50	2919.7 + 119.4	11.5 + 3.2	637.9 + 47.7
25	2805.1 + 176.7	9.8 + 2.8	700.3 + 62.5
12.5	2598.6 + 68.6	7.3 + 0.9	513.2 + 73.5
6.25	2449.2 + 830.6	6.9 + 1.4	440.4 + 29.5
3.13	3117.1 + 795.7	7.3 + 0.9	393.9 + 40.2
1.56	2481.0 + 719.3	6.0 + 1.8	358.4 + 74.8
no poly(I:C)	4.9 + 4.5	1.9+0.4	32.1 + 8.8
concentrations shown as pg/ml			

Table 12.

mAb 15 ($\mu\text{g/ml}$)	50.00	10.00	2.00	0.40	0.08	0.016	0.003	0
PIC	+	+	+	+	+	+	+	
IL-6	177.8 $\pm$ 5.6 *	214.6 + 3.6 *	359.2 + 57.6 *	727.2 + 50.5 *	10000 + 0	10000 + 0	10000 + 0	10000 + 0
CXCL8/IL-8	1040.7 $\pm$ 185.9	1765.9 + 97.1	6460.3 + 3684.4	57349.5 + 6293.4	72422.8 + 88279.2	47047.5 + 52393.1	76066.5 + 11354.1	196478.0 + 122298.4
CCL2/MCP-1	1187.7 $\pm$ 165.4 *	1955.4 + 72.7 *	9054.4 + 4110.9*	20000 + 0.0	20000 + 0.0	20000 + 0.0	20000 + 0.0	20000 + 0.0
IL-2R	25.0 $\pm$ 35.3 *	0.0 + 0.0 *	312.3 + 137.6 *	521.5 + 5.5	664.7 + 9.8	661.2 + 14.8	698.4 + 57.6	654.2 + 14.8
IL-15	0.0 $\pm$ 0.0 *	0.0 + 0.0 *	0.0 + 0.0*	4.1 + 0.0 *	38.8 + 6.5	43.4 + 0.0	38.8 + 6.5	43.4 + 0.0
IL-17	1.3 $\pm$ 1.8 *	11.8 + 16.8	11.8 + 16.8	27.9 + 6.0	47.4 + 10.4	54.3 + 20.2	40.0 + 0.0	51.2 + 5.1
IFN α	0.9 $\pm$ 1.3 *	0.9 + 1.3 *	19.0 + 7.7 *	36.1 + 0.0	44.9 + 1.7	41.2 + 3.5	47.3 + 1.7	40.0 + 1.8
CXCL10/IP-10	0.0 $\pm$ 0.0 *	58.1 + 2.6 *	633.0 + 471.6 *	1441.4 + 97.1	3023.8 + 166.1	2107.5 + 372.6	2346.4 + 226.1	2157.4 + 282.7
CCL4/MIP-1 β	0.0 $\pm$ 0.0 *	0.0 + 0.0 *	2.9 + 4.1 *	62.1 + 7.2*	176.6 + 21.3 *	227.5 + 19.9	248.3 + 19.4	281.7 + 37.5
RANTES	3.0 $\pm$ 0.0 *	15.4 + 4.5 *	201.1 + 169.1 *	952.4 + 41.1 *	2454.4 + 98.5 *	2698.1 + 88.6 *	2624.4 + 129.8 *	3459.7 + 181.8
TNF α	1.9 $\pm$ 0.4 *	1.6 + 0.0 *	2.2 + 0.0 *	3.4 + 0.0	6.3 + 0.5	8.5 + 0.0	7.6 + 1.4	6.9 + 2.3

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(continued)

mAb 15 (μg/ml)	50.00	10.00	2.00	0.40	0.08	0.016	0.003	0
VEGF	87.2 ± 8.7 *	28.6 ± 8.7 *	88.3 ± 52.1 *	156.1 ± 6.4 *	479.6 ± 14.1	544.6 ± 8.3	533.5 ± 70.2	607.3 ± 29.9
* Indicates significant p-values (less than 0.05) comparing mAb15 concentration vs. poly(I:C) alone Values are mean (pg/ml) ± SEM								

[0219] This suggested that TLR3 antibody antagonists can inhibit leukocyte trafficking and thus tissue damage caused by the influx of inflammatory cells.

[0220] For viability assays, HUVECs were cultured, plated and stimulated with poly(I:C) as described above. mAb 15EVQ dose-dependently restored poly(I:C)-induced reduction in HUVEC cell viability (Figure 24B).

[0221] Down-modulation of endothelial cell activation can suppress excessive immune cell infiltration and reduce tissue damage caused by cytokines that are increased during inflammatory conditions. Inflammation and overexpression of cytokines and adhesion molecules on endothelial cells are key contributors to developing atherosclerosis and hypertension. These data provide rationale for exploring the potential benefit of TLR3 antagonists for use in diseases of the blood vessels including vasculitides, and those featuring endothelial dysfunction. Another disease that is affected by inflammation and overexpressed cytokines is Kaposi's sarcoma (KS) that is common in immunosuppressed and HIV infected individuals and is caused by Kaposi's sarcoma herpes virus (KSHV). VEGF and cytokine production contribute to the survival of KS cells (Livengood et al., Cell Immunol. 249:55-62, 2007). TLR3 antagonists could be beneficial at reducing angiogenic risks associated with KS and other tumors and at preventing cell viability loss and protecting endothelial barrier integrity to prevent vascular leakage, a potentially serious condition associated with organ failure and life-threatening inflammatory conditions such as sepsis. TLR3 antagonism may also be beneficial in viral infections involving endothelial cell pathology such as the viral hemorrhagic fevers caused by members of the families flaviviridae (e.g. Dengue, yellow fever), filoviridae (Ebola, Marburg), bunyaviridae (e.g. Hantavirus, Nairovirus, Phlebovirus), and arenaviridae (e.g. Lujo, Lassa, Argentine, Bolivian, Venezuelan hemorrhagic fevers (Sihibamiya et al., Blood 113:714-722, 2009).

Example 19

Cross-reactivity of TLR3 antibody antagonists with cynomolgus and murine TLR3

[0222] Activity against cynomolgus or murine TLR3 were assessed using the ISRE reporter gene assay as described in Example 2. The cynomolgus (SEQ ID NO: 217) and murine TLR3 cDNAs (SEQ ID NO: 161) were amplified from whole blood and cloned into the pCEP4 vector (Clontech), and expressed as described above. mAb 15EVQ had IC50s of 4.18 μg/ml and 1.74 μg/ml in the cyno NF-κB and ISRE assays, respectively, compared to IC50s of 0.44 and 0.65 μg/ml in the human TLR3 NF-κB and ISRE assays, respectively. Isotype control antibodies had no effect in these assays.

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	Met	Arg	Gln	Thr	Leu	Pro	Cys	Ile	Tyr	Phe	Trp	Gly	Gly	Leu	Leu	Pro
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	Phe	Gly	Met	Leu	Cys	Ala	Ser	Ser	Thr	Thr	Lys	Cys	Thr	Val	Ser	His
				20					25					30		
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			35					40					45			
	Leu	Pro	Thr	Asn	Ile	Thr	Val	Leu	Asn	Leu	Thr	His	Asn	Gln	Leu	Arg
		50					55					60				
	Arg	Leu	Pro	Ala	Ala	Asn	Phe	Thr	Arg	Tyr	Ser	Gln	Leu	Thr	Ser	Leu
10	65					70					75					80
	Asp	Val	Gly	Phe	Asn	Thr	Ile	Ser	Lys	Leu	Glu	Pro	Glu	Leu	Cys	Gln
				85						90					95	
	Lys	Leu	Pro	Met	Leu	Lys	Val	Leu	Asn	Leu	Gln	His	Asn	Glu	Leu	Ser
				100					105					110		
15	Gln	Leu	Ser	Asp	Lys	Thr	Phe	Ala	Phe	Cys	Thr	Asn	Leu	Thr	Glu	Leu
			115				120						125			
	His	Leu	Met	Ser	Asn	Ser	Ile	Gln	Lys	Ile	Lys	Asn	Asn	Pro	Phe	Val
		130					135					140				
	Lys	Gln	Lys	Asn	Leu	Ile	Thr	Leu	Asp	Leu	Ser	His	Asn	Gly	Leu	Ser
	145					150					155					160
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				165						170					175	
	Leu	Leu	Ser	Asn	Asn	Lys	Ile	Gln	Ala	Leu	Lys	Ser	Glu	Glu	Leu	Asp
				180					185					190		
25	Ile	Phe	Ala	Asn	Ser	Ser	Leu	Lys	Lys	Leu	Glu	Leu	Ser	Ser	Asn	Gln
			195					200						205		
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		210					215						220			
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	225					230					235					240
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				245						250					255	
	Asn	Ser	Gln	Leu	Ser	Thr	Thr	Ser	Asn	Thr	Thr	Phe	Leu	Gly	Leu	Lys
				260					265					270		
	Trp	Thr	Asn	Leu	Thr	Met	Leu	Asp	Leu	Ser	Tyr	Asn	Asn	Leu	Asn	Val
			275					280						285		
35	Val	Gly	Asn	Asp	Ser	Phe	Ala	Trp	Leu	Pro	Gln	Leu	Glu	Tyr	Phe	Phe
		290					295					300				
	Leu	Glu	Tyr	Asn	Asn	Ile	Gln	His	Leu	Phe	Ser	His	Ser	Leu	His	Gly

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	Ile	Thr	His	His	Leu	Leu	Lys	Asp	Pro	Leu	Cys	Lys	Arg	Phe	Lys	Val
				820					825					830		
	His	His	Ala	Val	Gln	Gln	Ala	Ile	Glu	Gln	Asn	Leu	Asp	Ser	Ile	Ile
			835				840				845					
5	Leu	Val	Phe	Leu	Glu	Glu	Ile	Pro	Asp	Tyr	Lys	Leu	Asn	His	Ala	Leu
		850					855				860					
	Cys	Leu	Arg	Arg	Gly	Met	Phe	Lys	Ser	His	Cys	Ile	Leu	Asn	Trp	Pro
	865					870					875					880
10	Val	Gln	Lys	Glu	Arg	Ile	Gly	Ala	Phe	Arg	His	Lys	Leu	Gln	Val	Ala
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	Leu	Gly	Ser	Lys	Asn	Ser	Val	His								
				900												

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	Phe	Gly	Met	Leu	Cys	Ala	Ser	Ser	Thr	Thr	Lys	Cys	Thr	Val	Ser	His
				20					25					30		
5	Glu	Val	Ala	Asp	Cys	Ser	His	Leu	Lys	Leu	Thr	Gln	Val	Pro	Asp	Asp
			35					40					45			
	Leu	Pro	Thr	Asn	Ile	Thr	Val	Leu	Asn	Leu	Thr	His	Asn	Gln	Leu	Arg
			50				55					60				
	Arg	Leu	Pro	Ala	Ala	Asn	Phe	Thr	Arg	Tyr	Ser	Gln	Leu	Thr	Ser	Leu
	65					70					75					80
10	Asp	Val	Gly	Phe	Asn	Thr	Ile	Ser	Lys	Leu	Glu	Pro	Glu	Leu	Cys	Gln
				85					90						95	
	Lys	Leu	Pro	Met	Leu	Lys	Val	Leu	Asn	Leu	Gln	His	Asn	Glu	Leu	Ser
				100					105					110		
	Gln	Leu	Ser	Asp	Lys	Thr	Phe	Ala	Phe	Cys	Thr	Asn	Leu	Thr	Glu	Leu
				115				120					125			
15	His	Leu	Met	Ser	Asn	Ser	Ile	Gln	Lys	Ile	Lys	Asn	Asn	Pro	Phe	Val
							135					140				
	Lys	Gln	Lys	Asn	Leu	Ile	Thr	Leu	Asp	Leu	Ser	His	Asn	Gly	Leu	Ser
	145					150					155					160
	Ser	Thr	Lys	Leu	Gly	Thr	Gln	Val	Gln	Leu	Glu	Asn	Leu	Gln	Glu	Leu
20				165						170					175	
	Leu	Leu	Ser	Asn	Asn	Lys	Ile	Gln	Ala	Leu	Lys	Ser	Glu	Glu	Leu	Asp
				180					185					190		
	Ile	Phe	Ala	Asn	Ser	Ser	Leu	Lys	Lys	Leu	Glu	Leu	Ser	Ser	Asn	Gln
			195					200					205			
25	Ile	Lys	Glu	Phe	Ser	Pro	Gly	Cys	Phe	His	Ala	Ile	Gly	Arg	Leu	Phe
			210				215						220			
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	225					230					235					240
	Leu	Cys	Leu	Glu	Leu	Ala	Asn	Thr	Ser	Ile	Arg	Asn	Leu	Ser	Leu	Ser
					245					250					255	
30	Asn	Ser	Gln	Leu	Ser	Thr	Thr	Ser	Asn	Thr	Thr	Phe	Leu	Gly	Leu	Lys
				260					265					270		
	Trp	Thr	Asn	Leu	Thr	Met	Leu	Asp	Leu	Ser	Tyr	Asn	Asn	Leu	Asn	Val
			275					280					285			
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			290				295					300				
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						310					315					320
	Leu	Phe	Asn	Val	Arg	Tyr	Leu	Asn	Leu	Lys	Arg	Ser	Phe	Thr	Lys	Gln
				325						330					335	
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				340					345					350		
40	Trp	Leu	Lys	Cys	Leu	Glu	His	Leu	Asn	Met	Glu	Asp	Asn	Asp	Ile	Pro
			355					360					365			
	Gly	Ile	Lys	Ser	Asn	Met	Phe	Thr	Gly	Leu	Ile	Asn	Leu	Lys	Tyr	Leu
						375						380				
	Ser	Leu	Ser	Asn	Ser	Phe	Thr	Ser	Leu	Arg	Thr	Leu	Thr	Asn	Glu	Thr
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	Phe	Val	Ser	Leu	Ala	His	Ser	Pro	Leu	His	Ile	Leu	Asn	Leu	Thr	Lys
					405					410					415	
	Asn	Lys	Ile	Ser	Lys	Ile	Glu	Ser	Asp	Ala	Phe	Ser	Trp	Leu	Gly	His
				420					425					430		
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				435					440				445			
	Gly	Gln	Glu	Trp	Arg	Gly	Leu	Glu	Asn	Ile	Phe	Glu	Ile	Tyr	Leu	Ser
				450			455					460				
	Tyr	Asn	Lys	Tyr	Leu	Gln	Leu	Thr	Arg	Asn	Ser	Phe	Ala	Leu	Val	Pro
	465					470					475					480
55	Ser	Leu	Gln	Arg	Leu	Met	Leu	Arg	Arg	Val	Ala	Leu	Lys	Asn	Val	Asp
					485					490					495	
	Ser	Ser	Pro	Ser	Pro	Phe	Gln	Pro	Leu	Arg	Asn	Leu	Thr	Ile	Leu	Asp

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				500					505				510			
	Leu	Ser	Asn	Asn	Asn	Ile	Ala	Asn	Ile	Asn	Asp	Asp	Met	Leu	Glu	Gly
			515					520					525			
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			530					535					540			
	Leu	Trp	Lys	His	Ala	Asn	Pro	Gly	Gly	Pro	Ile	Tyr	Phe	Leu	Lys	Gly
	545					550					555					560
	Leu	Ser	His	Leu	His	Ile	Leu	Asn	Leu	Glu	Ser	Asn	Gly	Phe	Asp	Glu
				565						570						575
10	Ile	Pro	Val	Glu	Val	Phe	Lys	Asp	Leu	Phe	Glu	Leu	Lys	Ile	Ile	Asp
				580						585						590
	Leu	Gly	Leu	Asn	Asn	Leu	Asn	Thr	Leu	Pro	Ala	Ser	Val	Phe	Asn	Asn
			595					600					605			
	Gln	Val	Ser	Leu	Lys	Ser	Leu	Asn	Leu	Gln	Lys	Asn	Leu	Ile	Thr	Ser
15			610				615					620				
	Val	Glu	Lys	Lys	Val	Phe	Gly	Pro	Ala	Phe	Arg	Asn	Leu	Thr	Glu	Leu
	625					630					635					640
	Asp	Met	Arg	Phe	Asn	Pro	Phe	Asp	Cys	Thr	Cys	Glu	Ser	Ile	Ala	Trp
				645						650						655
20	Phe	Val	Asn	Trp	Ile	Asn	Glu	Thr	His	Thr	Asn	Ile	Pro	Glu	Leu	Ser
			660						665							670
	Ser	His	Tyr	Leu	Cys	Asn	Thr	Pro	Pro	His	Tyr	His	Gly	Phe	Pro	Val
			675					680					685			
	Arg	Leu	Phe	Asp	Thr	Ser	Ser	Cys	Lys	Asp	Ser	Ala	Pro	Phe	Glu	
		690					695					700				

<210> 5
 <211> 107
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> candidate 16 VL

<400> 5

	Asp	Ile	Gln	Met	Thr	Gln	Ser	Pro	Ser	Ser	Leu	Ser	Ala	Ser	Val	Gly
	1				5					10					15	
	Asp	Arg	Val	Thr	Ile	Thr	Cys	Arg	Ala	Ser	Gln	Gly	Ile	Ser	Ser	Trp
				20					25					30		
40	Leu	Asn	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Lys	Ala	Pro	Lys	Leu	Leu	Ile
			35				40						45			
	Tyr	Gly	Ala	Ser	Asn	Leu	Gln	Ser	Gly	Val	Pro	Ser	Arg	Phe	Ser	Gly
	50					55					60					
45	Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Thr	Ile	Ser	Ser	Leu	Gln	Pro
	65					70					75					80
	Glu	Asp	Phe	Ala	Val	Tyr	Tyr	Cys	Gln	Gln	Tyr	Asp	Asp	Phe	Ser	Ile
					85					90						95
	Thr	Phe	Gly	Gln	Gly	Thr	Lys	Val	Glu	Ile	Lys					
				100					105							

<210> 6
 <211> 116
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> candidate 16 VH

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<400> 6

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Gln Val Glu Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
 1 5 10 15
 Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Asn Asn Tyr
 20 25 30
 Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
 35 40 45
 Gly Ile Ile Asp Pro Gly Asp Ser Tyr Thr Asn Tyr Ala Pro Ser Phe
 50 55 60
 Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
 65 70 75 80
 Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
 85 90 95
 Ala Arg Asn Ile Tyr Glu Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val
 100 105 110
 Thr Val Ser Ser
 115

<210> 7

<211> 107

<212> PRT

<213> Artificial Sequence

<220>

<223> candidate 17 VL

<400> 7

Asp Ile Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ala Pro Gly Gln
 1 5 10 15
 Thr Ala Arg Ile Ser Cys Ser Gly Asp Ala Leu Gly Gly Tyr Phe Val
 20 25 30
 Ser Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr
 35 40 45
 Asp Asp Asp Asn Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
 50 55 60
 Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Glu
 65 70 75 80
 Asp Glu Ala Asp Tyr Tyr Cys Ala Ser Tyr Asp Gly Asp Glu Phe Thr
 85 90 95
 Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
 100 105

<210> 8

<211> 122

<212> PRT

<213> Artificial Sequence

<220>

<223> candidate 17 VH

<400> 8

EP 2 350 304 B1

5 Gln Val Glu Leu Gln Gln Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
 1 5 10 15
 Thr Leu Ser Leu Thr Cys Ala Ile Ser Gly Asp Ser Val Ser Thr Arg
 20 25 30
 Ser Ala Ala Trp Gly Trp Ile Arg Gln Ser Pro Gly Arg Gly Leu Glu
 35 40 45
 Trp Leu Gly Arg Ile Tyr Met Arg Ser Lys Trp Tyr Asn Asp Tyr Ala
 50 55 60
 Val Ser Val Lys Ser Arg Ile Thr Ile Asn Pro Asp Thr Ser Lys Asn
 65 70 75 80
 Gln Phe Ser Leu Gln Leu Asn Ser Val Thr Pro Glu Asp Thr Ala Val
 85 90 95
 Tyr Tyr Cys Ala Arg His Thr Tyr Pro Tyr Leu Ser Phe Asp Val Trp

15 Gly Gln Gly Thr Leu Val Thr Val Ser Ser
 100 105 110
 115 120

20 <210> 9
 <211> 108
 <212> PRT
 <213> Artificial Sequence

25 <220>
 <223> candidate 18 VL

<400> 9

30 Asp Ile Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ala Pro Gly Gln
 1 5 10 15
 Thr Ala Arg Ile Ser Cys Ser Gly Asp Asn Ile Gly Ser Tyr Tyr Val
 20 25 30
 His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr
 35 40 45
 Glu Asp Ser Glu Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
 50 55 60
 Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Glu
 65 70 75 80
 Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Ser Gln Phe Ser Phe
 85 90 95
 Gly Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
 100 105

45 <210> 10
 <211> 122
 <212> PRT
 <213> Artificial Sequence

50 <220>
 <223> candidate 18 VH

<400> 10

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EP 2 350 304 B1

	Gln	Val	Glu	Leu	Gln	Gln	Ser	Gly	Pro	Gly	Leu	Val	Lys	Pro	Ser	Gln
	1				5					10					15	
	Thr	Leu	Ser	Leu	Thr	Cys	Ala	Ile	Ser	Gly	Asp	Ser	Val	Ser	Ser	Asn
				20					25					30		
5	Ser	Ala	Ala	Trp	Gly	Trp	Ile	Arg	Gln	Ser	Pro	Gly	Arg	Gly	Leu	Glu
		35						40					45			
	Trp	Leu	Gly	Ile	Ile	Gln	Lys	Arg	Ser	Lys	Trp	Tyr	Asn	Asn	Tyr	Ala
	50						55					60				
	Val	Ser	Val	Lys	Ser	Arg	Ile	Thr	Ile	Asn	Pro	Asp	Thr	Ser	Lys	Asn
10	65					70					75					80
	Gln	Phe	Ser	Leu	Gln	Leu	Asn	Ser	Val	Thr	Pro	Glu	Asp	Thr	Ala	Val
					85					90					95	
	Tyr	Tyr	Cys	Ala	Arg	Tyr	Ser	Tyr	Pro	Phe	Tyr	Ser	Ile	Asp	Tyr	Trp
				100					105					110		
	Gly	Gln	Gly	Thr	Leu	Val	Thr	Val	Ser	Ser						
15			115					120								

<210> 11

<211> 107

<212> PRT

20 <213> Artificial Sequence

<220>

<223> candidate 19 VL

25 <400> 11

	Asp	Ile	Gln	Met	Thr	Gln	Ser	Pro	Ser	Ser	Leu	Ser	Ala	Ser	Val	Gly
	1				5					10					15	
	Asp	Arg	Val	Thr	Ile	Thr	Cys	Arg	Ala	Ser	Gln	Ser	Ile	Gly	Leu	Tyr
30				20					25					30		
	Leu	Ala	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Lys	Ala	Pro	Lys	Leu	Leu	Ile
		35						40					45			
	Tyr	Ala	Ala	Ser	Ser	Leu	Gln	Ser	Gly	Val	Pro	Ser	Arg	Phe	Ser	Gly
	50						55					60				
35	Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Thr	Ile	Ser	Ser	Leu	Gln	Pro
	65					70					75					80
	Glu	Asp	Phe	Ala	Thr	Tyr	Tyr	Cys	Gln	Gln	Tyr	Gly	Ser	Val	Ser	Ile
					85					90					95	
	Thr	Phe	Gly	Gln	Gly	Thr	Lys	Val	Glu	Ile	Lys					
40				100					105							

<210> 12

<211> 121

<212> PRT

45 <213> Artificial Sequence

<220>

<223> candidate 19 VH

50 <400> 12

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EP 2 350 304 B1

	Gln	Val	Glu	Leu	Val	Gln	Ser	Gly	Ala	Glu	Val	Lys	Lys	Pro	Gly	Glu
	1				5					10					15	
	Ser	Leu	Lys	Ile	Ser	Cys	Lys	Gly	Ser	Gly	Tyr	Ser	Phe	Thr	Asn	Tyr
				20					25					30		
5	Trp	Val	Gly	Trp	Val	Arg	Gln	Met	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Met
			35					40					45			
	Gly	Phe	Ile	Asp	Pro	Ser	Asp	Ser	Tyr	Thr	Asn	Tyr	Ala	Pro	Ser	Phe
		50					55					60				
	Gln	Gly	Gln	Val	Thr	Ile	Ser	Ala	Asp	Lys	Ser	Ile	Ser	Thr	Ala	Tyr
10	65					70					75					80
	Leu	Gln	Trp	Ser	Ser	Leu	Lys	Ala	Ser	Asp	Thr	Ala	Met	Tyr	Tyr	Cys
					85					90					95	
	Ala	Arg	Glu	Leu	Tyr	Gln	Gly	Tyr	Met	Asp	Thr	Phe	Asp	Ser	Trp	Gly
				100					105					110		
15	Gln	Gly	Thr	Leu	Val	Thr	Val	Ser	Ser							
			115					120								

<210> 13

<211> 108

<212> PRT

20 <213> Artificial Sequence

<220>

<223> candidate 1 VL

25 <400> 13

	Asp	Ile	Val	Leu	Thr	Gln	Ser	Pro	Ala	Thr	Leu	Ser	Leu	Ser	Pro	Gly
	1				5					10					15	
	Glu	Arg	Ala	Thr	Leu	Ser	Cys	Arg	Ala	Ser	Gln	Tyr	Ile	Asp	Ile	Ser
30				20					25					30		
	Tyr	Leu	Ala	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Gln	Ala	Pro	Arg	Leu	Leu
			35					40					45			
35	Ile	Tyr	Asp	Ala	Ser	Ser	Arg	Ala	Thr	Gly	Val	Pro	Ala	Arg	Phe	Ser
		50					55					60				
	Gly	Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Thr	Ile	Ser	Ser	Leu	Glu
	65					70					75					80
	Pro	Glu	Asp	Phe	Ala	Val	Tyr	Tyr	Cys	Gln	Gln	Tyr	Tyr	Ser	Leu	Ser
					85					90					95	
40	Ile	Thr	Phe	Gly	Gln	Gly	Thr	Lys	Val	Glu	Ile	Lys				
				100					105							

<210> 14

<211> 119

45 <212> PRT

<213> Artificial Sequence

<220>

<223> candidate 1 VH

50 <400> 14

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EP 2 350 304 B1

	Gly	Val	Glu	Leu	Val	Gln	Ser	Gly	Ala	Glu	Val	Lys	Lys	Pro	Gly	Glu
	1				5					10					15	
	Ser	Leu	Lys	Ile	Ser	Cys	Lys	Gly	Ser	Gly	Tyr	Ser	Phe	Thr	Asp	Asn
				20					25					30		
5	Trp	Ile	Ser	Trp	Val	Arg	Gln	Ala	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Met
			35					40					45			
	Gly	Val	Ile	Asp	Pro	Ser	Asp	Ser	Tyr	Thr	Asn	Tyr	Ala	Pro	Ser	Phe
		50					55					60				
	Gln	Gly	Gln	Val	Thr	Ile	Ser	Ala	Asp	Lys	Ser	Ile	Ser	Thr	Ala	Tyr
10		65				70					75					80
	Leu	Gln	Trp	Ser	Ser	Leu	Lys	Ala	Ser	Asp	Thr	Ala	Met	Tyr	Tyr	Cys
				85						90					95	
	Ala	Arg	Glu	Trp	Gly	Ile	Gly	Gly	Met	Val	Asp	Ile	Trp	Gly	Gln	Gly
				100					105					110		
15	Thr	Leu	Val	Thr	Val	Ser	Ser									
			115													

<210> 15

<211> 107

<212> PRT

20 <213> Artificial Sequence

<220>

<223> candidate 2 VL

25 <400> 15

	Asp	Ile	Gln	Met	Thr	Gln	Ser	Pro	Ser	Ser	Leu	Ser	Ala	Ser	Val	Gly
	1				5					10					15	
	Asp	Arg	Val	Thr	Ile	Thr	Cys	Arg	Ala	Ser	Gln	Gly	Ile	Ser	Ser	Trp
30				20					25					30		
	Leu	Asn	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Lys	Ala	Pro	Lys	Leu	Leu	Ile
			35					40					45			
	Tyr	Gly	Ala	Ser	Asn	Leu	Gln	Ser	Gly	Val	Pro	Ser	Arg	Phe	Ser	Gly
		50					55					60				
35	Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Thr	Ile	Ser	Ser	Leu	Gln	Pro
		65				70					75					80
	Glu	Asp	Phe	Ala	Val	Tyr	Tyr	Cys	Gln	Gln	Tyr	Asp	Asp	Phe	Ser	Ile
				85						90					95	
	Thr	Phe	Gly	Gln	Gly	Thr	Lys	Val	Glu	Ile	Lys					
40				100					105							

<210> 16

<211> 116

<212> PRT

45 <213> Artificial Sequence

<220>

<223> candidate 2 VH

50 <400> 16

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EP 2 350 304 B1

	Gln	Val	Glu	Leu	Val	Gln	Ser	Gly	Ala	Glu	Val	Lys	Lys	Pro	Gly	Glu
	1				5					10					15	
	Ser	Leu	Lys	Ile	Ser	Cys	Lys	Gly	Ser	Gly	Tyr	Ser	Phe	Asn	Asn	Tyr
				20					25					30		
5	Trp	Ile	Gly	Trp	Val	Arg	Gln	Met	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Met
			35					40					45			
	Gly	Ile	Ile	Asp	Pro	Gln	Asp	Ser	Trp	Thr	Asn	Tyr	Ala	Pro	Ser	Phe
		50					55					60				
	Gln	Gly	Gln	Val	Thr	Ile	Ser	Ala	Asp	Lys	Ser	Ile	Ser	Thr	Ala	Tyr
10		65				70					75					80
	Leu	Gln	Trp	Ser	Ser	Leu	Lys	Ala	Ser	Asp	Thr	Ala	Met	Tyr	Tyr	Cys
				85						90					95	
	Ala	Arg	Asn	Ile	Tyr	Glu	Phe	Asp	Tyr	Trp	Gly	Gln	Gly	Thr	Leu	Val
				100					105					110		
15	Thr	Val	Ser	Ser												
				115												

<210> 17

<211> 107

<212> PRT

20 <213> Artificial Sequence

<220>

<223> candidate 3 VL

25 <400> 17

	Asp	Ile	Glu	Leu	Thr	Gln	Pro	Pro	Ser	Val	Ser	Val	Ala	Pro	Gly	Gln
	1				5					10					15	
	Thr	Ala	Arg	Ile	Ser	Cys	Ser	Gly	Asp	Ala	Leu	Gly	Gly	Tyr	Phe	Val
30				20					25					30		
	Ser	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Gln	Ala	Pro	Val	Leu	Val	Ile	Tyr
			35					40					45			
	Asp	Asp	Asp	Asn	Arg	Pro	Ser	Gly	Ile	Pro	Glu	Arg	Phe	Ser	Gly	Ser
		50					55					60				
35	Asn	Ser	Gly	Asn	Thr	Ala	Thr	Leu	Thr	Ile	Ser	Gly	Thr	Gln	Ala	Glu
		65				70					75					80
	Asp	Glu	Ala	Asp	Tyr	Tyr	Cys	Ala	Ser	Tyr	Asp	Gly	Asp	Glu	Phe	Thr
				85						90				95		
	Val	Phe	Gly	Gly	Gly	Thr	Lys	Leu	Thr	Val	Leu					
40				100					105							

<210> 18

<211> 122

<212> PRT

45 <213> Artificial Sequence

<220>

<223> candidate 3 VH

50 <400> 18

Gln Val Glu Leu Gln Gln Ser Gly Pro Gly Leu Val Lys Pro Ser Gln

55

EP 2 350 304 B1

	1		5		10		15									
	Thr	Leu	Ser	Leu	Thr	Cys	Ala	Ile	Ser	Gly	Asp	Ser	Val	Ser	Thr	Arg
				20					25					30		
5	Ser	Ala	Ala	Trp	Gly	Trp	Ile	Arg	Gln	Ser	Pro	Gly	Arg	Gly	Leu	Glu
		35					40					45				
	Trp	Leu	Gly	Arg	Ile	His	Arg	Arg	Ser	Lys	Trp	Tyr	Asn	Asp	Tyr	Ala
	50					55						60				
	Val	Ser	Val	Lys	Ser	Arg	Ile	Thr	Ile	Asn	Pro	Asp	Thr	Ser	Lys	Asn
	65				70					75					80	
10	Gln	Phe	Ser	Leu	Gln	Leu	Asn	Ser	Val	Thr	Pro	Glu	Asp	Thr	Ala	Val
				85					90					95		
	Tyr	Tyr	Cys	Ala	Arg	His	Thr	Tyr	Pro	Tyr	Leu	Ser	Phe	Asp	Val	Trp
			100					105					110			
	Gly	Gln	Gly	Thr	Leu	Val	Thr	Val	Ser	Ser						
15			115				120									

<210> 19

<211> 107

<213> Artificial Sequence

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<220>

<223> candidate 4 VL

<400> 19

25

	Asp	Ile	Glu	Leu	Thr	Gln	Pro	Pro	Ser	Val	Ser	Val	Ala	Pro	Gly	Gln
	1				5				10					15		
	Thr	Ala	Arg	Ile	Ser	Cys	Ser	Gly	Asp	Ala	Leu	Gly	Gly	Tyr	Phe	Val
				20				25					30			
30	Ser	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Gln	Ala	Pro	Val	Leu	Val	Ile	Tyr
		35					40					45				
	Asp	Asp	Asp	Asn	Arg	Pro	Ser	Gly	Ile	Pro	Glu	Arg	Phe	Ser	Gly	Ser
	50					55					60					
	Asn	Ser	Gly	Asn	Thr	Ala	Thr	Leu	Thr	Ile	Ser	Gly	Thr	Gln	Ala	Glu
35	65			70					75					80		
	Asp	Glu	Ala	Asp	Tyr	Tyr	Cys	Ala	Ser	Tyr	Asp	Gly	Asp	Glu	Phe	Thr
				85				90					95			
	Val	Phe	Gly	Gly	Gly	Thr	Lys	Leu	Thr	Val	Leu					
			100					105								

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<210> 20

<211> 122

<212> PRT

<213> Artificial Sequence

45

<220>

<223> candidate 4 VH

<400> 20

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EP 2 350 304 B1

	Gln	Val	Glu	Leu	Gln	Gln	Ser	Gly	Pro	Gly	Leu	Val	Lys	Pro	Ser	Gln
	1				5					10					15	
	Thr	Leu	Ser	Leu	Thr	Cys	Ala	Ile	Ser	Gly	Asp	Ser	Val	Ser	Thr	Arg
5				20					25					30		
	Ser	Ala	Ala	Trp	Gly	Trp	Ile	Arg	Gln	Ser	Pro	Gly	Arg	Gly	Leu	Glu
			35					40					45			
	Trp	Leu	Gly	Lys	Ile	Ser	Tyr	Arg	Ser	Arg	Trp	Tyr	Asn	Asp	Tyr	Ala
	50					55						60				
10	Val	Ser	Val	Lys	Ser	Arg	Ile	Thr	Ile	Asn	Pro	Asp	Thr	Ser	Lys	Asn
	65					70					75					80
	Gln	Phe	Ser	Leu	Gln	Leu	Asn	Ser	Val	Thr	Pro	Glu	Asp	Thr	Ala	Val
					85					90					95	
	Tyr	Tyr	Cys	Ala	Arg	His	Thr	Tyr	Pro	Tyr	Leu	Ser	Phe	Asp	Val	Trp

15					100					105					110	
		Gly	Gln	Gly	Thr	Leu	Val	Thr	Val	Ser	Ser					
				115					120							

<210> 21
 <211> 107
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> candidate 5 VL

<400> 21

30	Asp	Ile	Glu	Leu	Thr	Gln	Pro	Pro	Ser	Val	Ser	Val	Ala	Pro	Gly	Gln
	1				5					10					15	
	Thr	Ala	Arg	Ile	Ser	Cys	Ser	Gly	Asp	Ala	Leu	Gly	Gly	Tyr	Phe	Val
				20					25					30		
	Ser	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Gln	Ala	Pro	Val	Leu	Val	Ile	Tyr
			35					40					45			
35	Asp	Asp	Asp	Asn	Arg	Pro	Ser	Gly	Ile	Pro	Glu	Arg	Phe	Ser	Gly	Ser
	50						55					60				
	Asn	Ser	Gly	Asn	Thr	Ala	Thr	Leu	Thr	Ile	Ser	Gly	Thr	Gln	Ala	Glu
	65					70					75					80
	Asp	Glu	Ala	Asp	Tyr	Tyr	Cys	Gln	Ser	Tyr	Asp	Glu	Asp	Ser	Ala	Thr
40					85					90					95	
	Val	Phe	Gly	Gly	Gly	Thr	Lys	Leu	Thr	Val	Leu					
				100					105							

<210> 22
 <211> 122
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> candidate 5 VH

<400> 22

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EP 2 350 304 B1

	Gln	Val	Glu	Leu	Gln	Gln	Ser	Gly	Pro	Gly	Leu	Val	Lys	Pro	Ser	Gln
	1				5					10					15	
	Thr	Leu	Ser	Leu	Thr	Cys	Ala	Ile	Ser	Gly	Asp	Ser	Val	Ser	Thr	Arg
				20					25					30		
5	Ser	Ala	Ala	Trp	Gly	Trp	Ile	Arg	Gln	Ser	Pro	Gly	Arg	Gly	Leu	Glu
		35						40					45			
	Trp	Leu	Gly	Arg	Ile	Tyr	Met	Arg	Ser	Lys	Trp	Tyr	Asn	Asp	Tyr	Ala
	50						55					60				
	Val	Ser	Val	Lys	Ser	Arg	Ile	Thr	Ile	Asn	Pro	Asp	Thr	Ser	Lys	Asn
10	65					70				75						80
	Gln	Phe	Ser	Leu	Gln	Leu	Asn	Ser	Val	Thr	Pro	Glu	Asp	Thr	Ala	Val
					85					90					95	
	Tyr	Tyr	Cys	Ala	Arg	His	Thr	Tyr	Pro	Tyr	Leu	Ser	Phe	Asp	Val	Trp
				100					105					110		
	Gly	Gln	Gly	Thr	Leu	Val	Thr	Val	Ser	Ser						
15			115					120								

<210> 23

<211> 107

<212> PRT

20 <213> Artificial Sequence

<220>

<223> candidate 6 VL

25 <400> 23

	Asp	Ile	Glu	Leu	Thr	Gln	Pro	Pro	Ser	Val	Ser	Val	Ala	Pro	Gly	Gln
	1				5					10					15	
	Thr	Ala	Arg	Ile	Ser	Cys	Ser	Gly	Asp	Ala	Leu	Gly	Gly	Tyr	Phe	Val
				20					25					30		
30	Ser	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Gln	Ala	Pro	Val	Leu	Val	Ile	Tyr
		35						40					45			
	Asp	Asp	Asp	Asn	Arg	Pro	Ser	Gly	Ile	Pro	Glu	Arg	Phe	Ser	Gly	Ser
	50						55					60				
35	Asn	Ser	Gly	Asn	Thr	Ala	Thr	Leu	Thr	Ile	Ser	Gly	Thr	Gln	Ala	Glu
	65					70				75						80
	Asp	Glu	Ala	Asp	Tyr	Tyr	Cys	Gly	Ser	Tyr	Asp	Ser	Asn	Ser	Leu	Thr
					85					90					95	
	Val	Phe	Gly	Gly	Gly	Thr	Lys	Leu	Thr	Val	Leu					
40				100					105							

<210> 24

<211> 122

<212> PRT

45 <213> Artificial Sequence

<220>

<223> candidate 6 VH

50 <400> 24

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EP 2 350 304 B1

	Gln	Val	Glu	Leu	Gln	Gln	Ser	Gly	Pro	Gly	Leu	Val	Lys	Pro	Ser	Gln
	1				5					10					15	
	Thr	Leu	Ser	Leu	Thr	Cys	Ala	Ile	Ser	Gly	Asp	Ser	Val	Ser	Thr	Arg
				20					25					30		
5	Ser	Ala	Ala	Trp	Gly	Trp	Ile	Arg	Gln	Ser	Pro	Gly	Arg	Gly	Leu	Glu
			35					40					45			
	Trp	Leu	Gly	Arg	Ile	Tyr	Met	Arg	Ser	Lys	Trp	Tyr	Asn	Asp	Tyr	Ala
	50					55						60				
	Val	Ser	Val	Lys	Ser	Arg	Ile	Thr	Ile	Asn	Pro	Asp	Thr	Ser	Lys	Asn
10	65					70					75					80
	Gln	Phe	Ser	Leu	Gln	Leu	Asn	Ser	Val	Thr	Pro	Glu	Asp	Thr	Ala	Val
					85					90					95	
	Tyr	Tyr	Cys	Ala	Arg	His	Thr	Tyr	Pro	Tyr	Leu	Ser	Phe	Asp	Val	Trp
				100					105					110		
	Gly	Gln	Gly	Thr	Leu	Val	Thr	Val	Ser	Ser						
15			115					120								

<210> 25

<211> 107

<212> PRT

20 <213> Artificial Sequence

<220>

<223> candidate 7 VL

25 <400> 25

	Asp	Ile	Glu	Leu	Thr	Gln	Pro	Pro	Ser	Val	Ser	Val	Ala	Pro	Gly	Gln
	1				5					10					15	
	Thr	Ala	Arg	Ile	Ser	Cys	Ser	Gly	Asp	Ala	Leu	Gly	Gly	Tyr	Phe	Val
30				20					25					30		
	Ser	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Gln	Ala	Pro	Val	Leu	Val	Ile	Tyr
			35					40					45			
	Asp	Asp	Asp	Asn	Arg	Pro	Ser	Gly	Ile	Pro	Glu	Arg	Phe	Ser	Gly	Ser
35																
		50					55					60				
	Asn	Ser	Gly	Asn	Thr	Ala	Thr	Leu	Thr	Ile	Ser	Gly	Thr	Gln	Ala	Glu
	65					70					75					80
	Asp	Glu	Ala	Asp	Tyr	Tyr	Cys	Ser	Ser	Tyr	Asp	Ser	Asp	Ser	Leu	Thr
					85					90					95	
40	Val	Phe	Gly	Gly	Gly	Thr	Lys	Leu	Thr	Val	Leu					
				100					105							

<210> 26

<211> 122

45 <212> PRT

<213> Artificial Sequence

<220>

<223> candidate 7 VH

50 <400> 26

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	Gln	Val	Glu	Leu	Gln	Gln	Ser	Gly	Pro	Gly	Leu	Val	Lys	Pro	Ser	Gln
	1				5					10					15	
	Thr	Leu	Ser	Leu	Thr	Cys	Ala	Ile	Ser	Gly	Asp	Ser	Val	Ser	Thr	Arg
				20					25					30		
5	Ser	Ala	Ala	Trp	Gly	Trp	Ile	Arg	Gln	Ser	Pro	Gly	Arg	Gly	Leu	Glu
			35					40					45			
	Trp	Leu	Gly	Arg	Ile	Tyr	Met	Arg	Ser	Lys	Trp	Tyr	Asn	Asp	Tyr	Ala
	50					55						60				
	Val	Ser	Val	Lys	Ser	Arg	Ile	Thr	Ile	Asn	Pro	Asp	Thr	Ser	Lys	Asn
10	65					70					75					80
	Gln	Phe	Ser	Leu	Gln	Leu	Asn	Ser	Val	Thr	Pro	Glu	Asp	Thr	Ala	Val
					85					90					95	
	Tyr	Tyr	Cys	Ala	Arg	His	Thr	Tyr	Pro	Tyr	Leu	Ser	Phe	Asp	Val	Trp
				100					105					110		
	Gly	Gln	Gly	Thr	Leu	Val	Thr	Val	Ser	Ser						
15			115					120								

<210> 27

<211> 108

<212> PRT

20 <213> Artificial Sequence

<220>

<223> candidate 8 VL

25 <400> 27

	Asp	Ile	Glu	Leu	Thr	Gln	Pro	Pro	Ser	Val	Ser	Val	Ala	Pro	Gly	Gln
	1				5					10					15	
	Thr	Ala	Arg	Ile	Ser	Cys	Ser	Gly	Asp	Asn	Ile	Gly	Ser	Tyr	Tyr	Val
				20					25					30		
30	His	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Gln	Ala	Pro	Val	Leu	Val	Ile	Tyr
			35					40					45			
	Glu	Asp	Ser	Glu	Arg	Pro	Ser	Gly	Ile	Pro	Glu	Arg	Phe	Ser	Gly	Ser
	50						55					60				
35	Asn	Ser	Gly	Asn	Thr	Ala	Thr	Leu	Thr	Ile	Ser	Gly	Thr	Gln	Ala	Glu
	65					70					75					80
	Asp	Glu	Ala	Asp	Tyr	Tyr	Cys	Gln	Ser	Tyr	Asp	Ser	Gln	Phe	Ser	Phe
					85					90					95	
	Gly	Val	Phe	Gly	Gly	Gly	Thr	Lys	Leu	Thr	Val	Leu				
40				100					105							

<210> 28

<211> 122

<212> PRT

45 <213> Artificial Sequence

<220>

<223> candidate 8 VH

50 <400> 28

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EP 2 350 304 B1

	Gln	Val	Glu	Leu	Gln	Gln	Ser	Gly	Pro	Gly	Leu	Val	Lys	Pro	Ser	Gln
	1				5					10					15	
	Thr	Leu	Ser	Leu	Thr	Cys	Ala	Ile	Ser	Gly	Asp	Ser	Val	Ser	Ser	Asn
				20					25					30		
5	Ser	Ala	Ala	Trp	Gly	Trp	Ile	Arg	Gln	Ser	Pro	Gly	Arg	Gly	Leu	Glu
			35					40					45			
	Trp	Leu	Gly	Ile	Ile	Gln	Thr	Arg	Ser	Lys	Trp	Tyr	Asn	Asp	Tyr	Ala
	50						55					60				
	Val	Ser	Val	Lys	Ser	Arg	Ile	Thr	Ile	Asn	Pro	Asp	Thr	Ser	Lys	Asn
10	65					70					75					80
	Gln	Phe	Ser	Leu	Gln	Leu	Asn	Ser	Val	Thr	Pro	Glu	Asp	Thr	Ala	Val
					85					90					95	
	Tyr	Tyr	Cys	Ala	Arg	Tyr	Ser	Tyr	Pro	Phe	Tyr	Ser	Ile	Asp	Tyr	Trp
				100					105					110		
	Gly	Gln	Gly	Thr	Leu	Val	Thr	Val	Ser	Ser						
15			115					120								

<210> 29

<211> 108

<212> PRT

20 <213> Artificial Sequence

<220>

<223> candidate 9 VL

25 <400> 29

	Asp	Ile	Glu	Leu	Thr	Gln	Pro	Pro	Ser	Val	Ser	Val	Ala	Pro	Gly	Gln
	1				5					10					15	
	Thr	Ala	Arg	Ile	Ser	Cys	Ser	Gly	Asp	Asn	Ile	Gly	Ser	Tyr	Tyr	Val
				20					25					30		
30	His	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Gln	Ala	Pro	Val	Leu	Val	Ile	Tyr
			35					40					45			
	Glu	Asp	Ser	Glu	Arg	Pro	Ser	Gly	Ile	Pro	Glu	Arg	Phe	Ser	Gly	Ser
	50						55					60				
35	Asn	Ser	Gly	Asn	Thr	Ala	Thr	Leu	Thr	Ile	Ser	Gly	Thr	Gln	Ala	Glu
	65					70					75					80
	Asp	Glu	Ala	Asp	Tyr	Tyr	Cys	Gln	Ser	Tyr	Asp	Ser	Gln	Phe	Ser	Phe
					85					90				95		
	Gly	Val	Phe	Gly	Gly	Gly	Thr	Lys	Leu	Thr	Val	Leu				
40				100					105							

<210> 30

<211> 122

<212> PRT

45 <213> Artificial Sequence

<220>

<223> candidate 9 VH

50 <400> 30

	Gln	Val	Glu	Leu	Gln	Gln	Ser	Gly	Pro	Gly	Leu	Val	Lys	Pro	Ser	Gln
	1				5					10					15	
	Thr	Leu	Ser	Leu	Thr	Cys	Ala	Ile	Ser	Gly	Asp	Ser	Val	Ser	Ser	Asn
				20					25					30		

55

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Ser Ala Ala Trp Gly Trp Ile Arg Gln Ser Pro Gly Arg Gly Leu Glu
 35 40 45
 Trp Leu Gly Ile Ile Gln Ile Arg Ser Lys Trp Tyr Asn Asp Tyr Ala
 50 55 60
 5 Leu Ser Val Lys Ser Arg Ile Thr Ile Asn Pro Asp Thr Ser Lys Asn
 65 70 75 80
 Gln Phe Ser Leu Gln Leu Asn Ser Val Thr Pro Glu Asp Thr Ala Val
 85 90 95
 Tyr Tyr Cys Ala Arg Tyr Ser Tyr Pro Phe Tyr Ser Ile Asp Tyr Trp
 10 100 105 110
 Gly Gln Gly Thr Leu Val Thr Val Ser Ser
 115 120

<210> 31
 <211> 107
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> candidate 10 VL

<400> 31

Asp Ile Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ala Pro Gly Gln
 1 5 10 15
 Thr Ala Arg Ile Ser Cys Ser Gly Asp Asn Ile Gly Ser Tyr Tyr Val
 20 25 30
 His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr
 35 40 45
 30 Glu Asp Ser Glu Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
 50 55 60
 Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Glu
 65 70 75 80
 Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Thr Pro Val Tyr Ser
 85 90 95
 35 Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
 100 105

<210> 32
 <211> 122
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> candidate 10 VH

<400> 32

EP 2 350 304 B1

5 Gln Val Glu Leu Gln Gln Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
 1 5 10 15
 Thr Leu Ser Leu Thr Cys Ala Ile Ser Gly Asp Ser Val Ser Ser Asn
 20 25 30
 Ser Ala Ala Trp Gly Trp Ile Arg Gln Ser Pro Gly Arg Gly Leu Glu
 35 40 45
 Trp Leu Gly Ile Ile Gln Lys Arg Ser Lys Trp Tyr Asn Asn Tyr Ala
 50 55 60
 10 Val Ser Val Lys Ser Arg Ile Thr Ile Asn Pro Asp Thr Ser Lys Asn
 65 70 75 80
 Gln Phe Ser Leu Gln Leu Asn Ser Val Thr Pro Glu Asp Thr Ala Val
 85 90 95
 Tyr Tyr Cys Ala Arg Tyr Ser Tyr Pro Phe Tyr Ser Ile Asp Tyr Trp
 100 105 110
 15 Gly Gln Gly Thr Leu Val Thr Val Ser Ser

115

120

20 <210> 33
 <211> 107
 <212> PRT
 <213> Artificial Sequence

25 <220>
 <223> candidate 11 VL

<400> 33

30 Asp Ile Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ala Pro Gly Gln
 1 5 10 15
 Thr Ala Arg Ile Ser Cys Ser Gly Asp Asn Ile Gly Ser Tyr Tyr Val
 20 25 30
 35 His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr
 35 40 45
 Glu Asp Ser Glu Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
 50 55 60
 Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Glu
 65 70 75 80
 40 Asp Glu Ala Asp Tyr Tyr Cys Ser Ser Tyr Asp Glu Pro Asn Phe Asn
 85 90 95
 Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
 100 105

45 <210> 34
 <211> 122
 <212> PRT
 <213> Artificial Sequence

50 <220>
 <223> candidate 11 VH

<400> 34

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EP 2 350 304 B1

	Gln	Val	Glu	Leu	Gln	Gln	Ser	Gly	Pro	Gly	Leu	Val	Lys	Pro	Ser	Gln
	1				5					10					15	
	Thr	Leu	Ser	Leu	Thr	Cys	Ala	Ile	Ser	Gly	Asp	Ser	Val	Ser	Ser	Asn
				20					25					30		
5	Ser	Ala	Ala	Trp	Gly	Trp	Ile	Arg	Gln	Ser	Pro	Gly	Arg	Gly	Leu	Glu
		35						40					45			
	Trp	Leu	Gly	Ile	Ile	Gln	Lys	Arg	Ser	Lys	Trp	Tyr	Asn	Asn	Tyr	Ala
	50						55					60				
	Val	Ser	Val	Lys	Ser	Arg	Ile	Thr	Ile	Asn	Pro	Asp	Thr	Ser	Lys	Asn
10	65					70					75					80
	Gln	Phe	Ser	Leu	Gln	Leu	Asn	Ser	Val	Thr	Pro	Glu	Asp	Thr	Ala	Val
					85					90					95	
	Tyr	Tyr	Cys	Ala	Arg	Tyr	Ser	Tyr	Pro	Phe	Tyr	Ser	Ile	Asp	Tyr	Trp
				100					105					110		
	Gly	Gln	Gly	Thr	Leu	Val	Thr	Val	Ser	Ser						
15			115					120								

<210> 35

<211> 122

<212> PRT

20 <213> Artificial Sequence

<220>

<223> candidate 12 VL

25 <400> 35

	Asp	Ile	Glu	Leu	Gln	Gln	Ser	Gly	Pro	Gly	Leu	Val	Lys	Pro	Ser	Gln
	1				5					10					15	
	Thr	Leu	Ser	Leu	Thr	Cys	Ala	Ile	Ser	Gly	Asp	Ser	Val	Ser	Ser	Asn
				20					25					30		
30	Ser	Ala	Ala	Trp	Gly	Trp	Ile	Arg	Gln	Ser	Pro	Gly	Arg	Gly	Leu	Glu
		35						40					45			
	Trp	Leu	Gly	Ile	Ile	Gln	Lys	Arg	Ser	Lys	Trp	Tyr	Asn	Asn	Tyr	Ala
	50						55					60				
	Val	Ser	Val	Lys	Ser	Arg	Ile	Thr	Ile	Asn	Pro	Asp	Thr	Ser	Lys	Asn
35	65					70					75					80
	Gln	Phe	Ser	Leu	Gln	Leu	Asn	Ser	Val	Thr	Pro	Glu	Asp	Thr	Ala	Val
					85					90					95	
	Tyr	Tyr	Cys	Ala	Arg	Tyr	Ser	Tyr	Pro	Phe	Tyr	Ser	Ile	Asp	Tyr	Trp
				100					105					110		
40	Gly	Gln	Gly	Thr	Leu	Val	Thr	Val	Ser	Ser						
			115					120								

<210> 36

<211> 122

45 <212> PRT

<213> Artificial Sequence

<220>

<223> candidate 12 VH

50 <400> 36

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EP 2 350 304 B1

	Gln	Val	Glu	Leu	Gln	Gln	Ser	Gly	Pro	Gly	Leu	Val	Lys	Pro	Ser	Gln
	1				5					10					15	
	Thr	Leu	Ser	Leu	Thr	Cys	Ala	Ile	Ser	Gly	Asp	Ser	Val	Ser	Ser	Asn
				20					25					30		
5	Ser	Ala	Ala	Trp	Gly	Trp	Ile	Arg	Gln	Ser	Pro	Gly	Arg	Gly	Leu	Glu
		35						40					45			
	Trp	Leu	Gly	Ile	Ile	Gln	Lys	Arg	Ser	Lys	Trp	Tyr	Asn	Asn	Tyr	Ala
	50						55					60				
	Val	Ser	Val	Lys	Ser	Arg	Ile	Thr	Ile	Asn	Pro	Asp	Thr	Ser	Lys	Asn
10	65					70					75					80
	Gln	Phe	Ser	Leu	Gln	Leu	Asn	Ser	Val	Thr	Pro	Glu	Asp	Thr	Ala	Val
					85					90					95	
	Tyr	Tyr	Cys	Ala	Arg	Tyr	Ser	Tyr	Pro	Phe	Tyr	Ser	Ile	Asp	Tyr	Trp
				100					105					110		
	Gly	Gln	Gly	Thr	Leu	Val	Thr	Val	Ser	Ser						
15			115					120								

<210> 37

<211> 107

<212> PRT

20 <213> Artificial Sequence

<220>

<223> candidate 13 VL

25 <400> 37

	Asp	Ile	Gln	Met	Thr	Gln	Ser	Pro	Ser	Ser	Leu	Ser	Ala	Ser	Val	Gly
	1				5					10					15	
	Asp	Arg	Val	Thr	Ile	Thr	Cys	Arg	Ala	Ser	Gln	Ser	Ile	Gly	Leu	Tyr
30				20					25					30		
	Leu	Ala	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Lys	Ala	Pro	Lys	Leu	Leu	Ile
		35						40					45			
	Tyr	Ala	Ala	Ser	Ser	Leu	Gln	Ser	Gly	Val	Pro	Ser	Arg	Phe	Ser	Gly
35			50					55					60			
	Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Thr	Ile	Ser	Ser	Leu	Gln	Pro
	65					70					75					80
	Glu	Asp	Phe	Ala	Thr	Tyr	Tyr	Cys	Gln	Gln	Gly	Glu	Ser	Ile	Leu	Ser
					85					90					95	
40	Thr	Phe	Gly	Gln	Gly	Thr	Lys	Val	Glu	Ile	Lys					
				100					105							

<210> 38

<211> 121

45 <212> PRT

<213> Artificial Sequence

<220>

<223> candidate 13 VH

50 <400> 38

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	Gln	Val	Glu	Leu	Val	Gln	Ser	Gly	Ala	Glu	Val	Lys	Lys	Pro	Gly	Glu
	1				5					10					15	
	Ser	Leu	Lys	Ile	Ser	Cys	Lys	Gly	Ser	Gly	Tyr	Ser	Phe	Thr	Asn	Tyr
				20					25					30		
5	Trp	Val	Gly	Trp	Val	Arg	Gln	Met	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Met
			35					40					45			
	Gly	Phe	Ile	Asp	Pro	Ser	Asp	Ser	Tyr	Thr	Asn	Tyr	Ala	Pro	Ser	Phe
		50					55					60				
	Gln	Gly	Gln	Val	Thr	Ile	Ser	Ala	Asp	Lys	Ser	Ile	Ser	Thr	Ala	Tyr
10		65				70					75					80
	Leu	Gln	Trp	Ser	Ser	Leu	Lys	Ala	Ser	Asp	Thr	Ala	Met	Tyr	Tyr	Cys
					85					90					95	
	Ala	Arg	Glu	Leu	Tyr	Gln	Gly	Tyr	Met	Asp	Thr	Phe	Asp	Ser	Trp	Gly
				100					105					110		
15	Gln	Gly	Thr	Leu	Val	Thr	Val	Ser	Ser							
			115					120								

<210> 39

<211> 107

<212> PRT

20 <213> Artificial Sequence

<220>

<223> candidate 14 VL

25 <400> 39

	Asp	Ile	Gln	Met	Thr	Gln	Ser	Pro	Ser	Ser	Leu	Ser	Ala	Ser	Val	Gly
	1				5					10					15	
	Asp	Arg	Val	Thr	Ile	Thr	Cys	Arg	Ala	Ser	Gln	Ser	Ile	Gly	Leu	Tyr
30				20					25					30		
	Leu	Ala	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Lys	Ala	Pro	Lys	Leu	Leu	Ile
			35					40					45			
	Tyr	Ala	Ala	Ser	Ser	Leu	Gln	Ser	Gly	Val	Pro	Ser	Arg	Phe	Ser	Gly
		50					55					60				
35	Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Thr	Ile	Ser	Ser	Leu	Gln	Pro
		65				70					75					80
	Glu	Asp	Phe	Ala	Thr	Tyr	Tyr	Cys	Gln	Gln	Ala	Glu	Thr	Val	Ser	Pro
					85					90					95	
40	Thr	Phe	Gly	Gln	Gly	Thr	Lys	Val	Glu	Ile	Lys					
				100					105							

<210> 40

<211> 121

<212> PRT

45 <213> Artificial Sequence

<220>

<223> candidate 14 VH

50 <400> 40

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EP 2 350 304 B1

	Gln	Val	Glu	Leu	Val	Gln	Ser	Gly	Ala	Glu	Val	Lys	Lys	Pro	Gly	Glu
	1				5					10					15	
	Ser	Leu	Lys	Ile	Ser	Cys	Lys	Gly	Ser	Gly	Tyr	Ser	Phe	Thr	Asn	Tyr
				20					25					30		
5	Trp	Val	Gly	Trp	Val	Arg	Gln	Met	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Met
			35					40					45			
	Gly	Phe	Ile	Asp	Pro	Ser	Asp	Ser	Tyr	Thr	Asn	Tyr	Ala	Pro	Ser	Phe
		50					55					60				
	Gln	Gly	Gln	Val	Thr	Ile	Ser	Ala	Asp	Lys	Ser	Ile	Ser	Thr	Ala	Tyr
10		65				70					75					80
	Leu	Gln	Trp	Ser	Ser	Leu	Lys	Ala	Ser	Asp	Thr	Ala	Met	Tyr	Tyr	Cys
					85					90					95	
	Ala	Arg	Glu	Leu	Tyr	Gln	Gly	Tyr	Met	Asp	Thr	Phe	Asp	Ser	Trp	Gly
				100					105					110		
15	Gln	Gly	Thr	Leu	Val	Thr	Val	Ser	Ser							
			115					120								

<210> 41

<211> 107

<212> PRT

20 <213> Artificial Sequence

<220>

<223> candidate 15 VL

25 <400> 41

	Asp	Ile	Gln	Met	Thr	Gln	Ser	Pro	Ser	Ser	Leu	Ser	Ala	Ser	Val	Gly
	1				5					10					15	
	Asp	Arg	Val	Thr	Ile	Thr	Cys	Arg	Ala	Ser	Gln	Ser	Ile	Gly	Leu	Tyr
30				20					25					30		
	Leu	Ala	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Lys	Ala	Pro	Lys	Leu	Leu	Ile
			35					40					45			
	Tyr	Ala	Ala	Ser	Ser	Leu	Gln	Ser	Gly	Val	Pro	Ser	Arg	Phe	Ser	Gly
		50					55					60				
35	Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Thr	Ile	Ser	Ser	Leu	Gln	Pro
		65				70					75					80
	Glu	Asp	Phe	Ala	Thr	Tyr	Tyr	Cys	Gln	Gln	Gly	Asn	Thr	Leu	Ser	Tyr
					85					90					95	
40	Thr	Phe	Gly	Gln	Gly	Thr	Lys	Val	Glu	Ile	Lys					
				100					105							

<210> 42

<211> 121

<212> PRT

45 <213> Artificial Sequence

<220>

<223> candidate 15 VH

50 <400> 42

	Gln	Val	Glu	Leu	Val	Gln	Ser	Gly	Ala	Glu	Val	Lys	Lys	Pro	Gly	Glu
	1				5					10					15	
	Ser	Leu	Lys	Ile	Ser	Cys	Lys	Gly	Ser	Gly	Tyr	Ser	Phe	Thr	Asn	Tyr
55				20					25					30		

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	Trp	Val	Gly	Trp	Val	Arg	Gln	Met	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Met
			35					40					45			
	Gly	Phe	Ile	Asp	Pro	Ser	Asp	Ser	Tyr	Thr	Asn	Tyr	Ala	Pro	Ser	Phe
	50						55					60				
5	Gln	Gly	Gln	Val	Thr	Ile	Ser	Ala	Asp	Lys	Ser	Ile	Ser	Thr	Ala	Tyr
	65					70					75					80
	Leu	Gln	Trp	Ser	Ser	Leu	Lys	Ala	Ser	Asp	Thr	Ala	Met	Tyr	Tyr	Cys
					85					90					95	
	Ala	Arg	Glu	Leu	Tyr	Gln	Gly	Tyr	Met	Asp	Thr	Phe	Asp	Ser	Trp	Gly
10				100					105					110		
	Gln	Gly	Thr	Leu	Val	Thr	Val	Ser	Ser							
			115					120								

15 <210> 43
 <211> 7
 <212> PRT
 <213> Artificial Sequence

20 <220>
 <223> candidate 1 LCDR1
 <400> 43

	Gln	Tyr	Ile	Asp	Ile	Ser	Tyr
25	1				5		

30 <210> 44
 <211> 3
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> candidate 1 LCDR2
 35 <400> 44

Asp	Ala	Ser
1		

40 <210> 45
 <211> 9
 <212> PRT
 <213> Artificial Sequence

45 <220>
 <223> candidate 1 LCDR3
 <400> 45

Gln	Gln	Tyr	Tyr	Ser	Leu	Ser	Ile	Thr
1				5				

55 <210> 46
 <211> 8
 <212> PRT
 <213> Artificial Sequence

<220>

EP 2 350 304 B1

<223> candidate 1 HCDR1

<400> 46

5

Gly Tyr Ser Phe Thr Asp Asn Trp

10

1

5

<210> 47

<211> 8

<212> PRT

15

<213> Artificial Sequence

<220>

<223> candidate 1 HCDR2

20

<400> 47

Ile Asp Pro Ser Asp Ser Gln Thr

1

5

25

<210> 48

<211> 12

<212> PRT

<213> Artificial Sequence

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<220>

<223> candidate 1 HCDR3

<400> 48

35

Ala Arg Glu Trp Gly Ile Gly Gly Met Val Asp Ile

1

5

10

<210> 49

40

<211> 6

<212> PRT

<213> Artificial Sequence

<220>

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<223> candidate 2 LCDR1

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Gly Tyr Ser Phe Asn Asn Tyr Trp
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Ala Arg Tyr Ser Tyr Pro Phe Tyr Ser Ile Asp Tyr
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Gln Ser Tyr Asp Thr Pro Val Tyr Ser Val
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Ser Ser Tyr Asp Asp Pro Asn Phe Gln Val

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Gln Ser Ile Gly Leu Tyr
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Ala Ala Ser
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Gly Tyr Ser Phe Thr Asn Tyr Trp
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Ile Asp Pro Ser Asp Ser Tyr Thr
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Ala Arg Glu Leu Tyr Gln Gly Tyr Met Asp Thr Phe Asp Ser
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<223> Candidate 14 LCDR3

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Gln Gln Ala Glu Thr Val Ser Pro Thr
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10 <220>
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20 <210> 87
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25 <400> 87

Gln Gln Gly Asn Thr Leu Ser Tyr Thr
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30 <210> 88
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35 <220>
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45 <210> 89
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50 <400> 89

Gln Gln Tyr Gly Ser Val Ser Ile Thr
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55 <210> 90
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<213> Artificial Sequence

<220>

<223> Candidate 16 Full length heavy chain

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Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Asn Asn Tyr
 20           25           30
Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
 35           40           45
Gly Ile Ile Asp Pro Gly Asp Ser Tyr Thr Asn Tyr Ala Pro Ser Phe
 50           55           60
Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
 65           70           75           80
Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
 85           90           95
Ala Arg Asn Ile Tyr Glu Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val
 100          105          110
Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala
 115          120          125
Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu
 130          135          140
Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly
 145          150          155          160
Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser

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				165				170					175			
	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val	Pro	Ser	Ser	Ser	Leu
				180					185				190			
5	Gly	Thr	Lys	Thr	Tyr	Thr	Cys	Asn	Val	Asp	His	Lys	Pro	Ser	Asn	Thr
			195					200					205			
	Lys	Val	Asp	Lys	Arg	Val	Glu	Ser	Lys	Tyr	Gly	Pro	Pro	Cys	Pro	Pro
		210					215					220				
	Cys	Pro	Ala	Pro	Glu	Phe	Leu	Gly	Gly	Pro	Ser	Val	Phe	Leu	Phe	Pro
		225				230					235					240
10	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser	Arg	Thr	Pro	Glu	Val	Thr
				245						250						255
	Cys	Val	Val	Val	Asp	Val	Ser	Gln	Glu	Asp	Pro	Glu	Val	Gln	Phe	Asn
			260						265					270		
	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn	Ala	Lys	Thr	Lys	Pro	Arg
			275					280					285			
15	Glu	Glu	Gln	Phe	Asn	Ser	Thr	Tyr	Arg	Val	Val	Ser	Val	Leu	Thr	Val
		290					295					300				
	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu	Tyr	Lys	Cys	Lys	Val	Ser
		305				310					315					320
	Asn	Lys	Gly	Leu	Pro	Ser	Ser	Ile	Glu	Lys	Thr	Ile	Ser	Lys	Ala	Lys
20				325						330					335	
	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr	Leu	Pro	Pro	Ser	Gln	Glu
				340					345					350		
	Glu	Met	Thr	Lys	Asn	Gln	Val	Ser	Leu	Thr	Cys	Leu	Val	Lys	Gly	Phe
			355					360					365			
25	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu	Ser	Asn	Gly	Gln	Pro	Glu
		370					375					380				
	Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Val	Leu	Asp	Ser	Asp	Gly	Ser	Phe
		385				390					395					400
	Phe	Leu	Tyr	Ser	Arg	Leu	Thr	Val	Asp	Lys	Ser	Arg	Trp	Gln	Glu	Gly
				405						410					415	
30	Asn	Val	Phe	Ser	Cys	Ser	Val	Met	His	Glu	Ala	Leu	His	Asn	His	Tyr
			420						425					430		
	Thr	Gln	Lys	Ser	Leu	Ser	Leu	Ser	Leu	Gly	Lys					
			435				440									

35 <210> 91
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40 <220>
 <223> Candidate 17 Full length heavy chain

<400> 91

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	1				5					10					15	
	Thr	Leu	Ser	Leu	Thr	Cys	Ala	Ile	Ser	Gly	Asp	Ser	Val	Ser	Thr	Arg
				20					25					30		
5	Ser	Ala	Ala	Trp	Gly	Trp	Ile	Arg	Gln	Ser	Pro	Gly	Arg	Gly	Leu	Glu
			35					40					45			
	Trp	Leu	Gly	Arg	Ile	Tyr	Met	Arg	Ser	Lys	Trp	Tyr	Asn	Asp	Tyr	Ala
		50					55					60				
	Val	Ser	Val	Lys	Ser	Arg	Ile	Thr	Ile	Asn	Pro	Asp	Thr	Ser	Lys	Asn
10	65					70					75					80
	Gln	Phe	Ser	Leu	Gln	Leu	Asn	Ser	Val	Thr	Pro	Glu	Asp	Thr	Ala	Val
					85					90					95	
	Tyr	Tyr	Cys	Ala	Arg	His	Thr	Tyr	Pro	Tyr	Leu	Ser	Phe	Asp	Val	Trp
				100					105					110		
15	Gly	Gln	Gly	Thr	Leu	Val	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro
			115					120						125		
	Ser	Val	Phe	Pro	Leu	Ala	Pro	Cys	Ser	Arg	Ser	Thr	Ser	Glu	Ser	Thr
		130					135					140				
20	Ala	Ala	Leu	Gly	Cys	Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr
	145					150					155					160
	Val	Ser	Trp	Asn	Ser	Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro
				165						170					175	
	Ala	Val	Leu	Gln	Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr
				180					185					190		
25	Val	Pro	Ser	Ser	Ser	Leu	Gly	Thr	Lys	Thr	Tyr	Thr	Cys	Asn	Val	Asp
			195					200					205			
	His	Lys	Pro	Ser	Asn	Thr	Lys	Val	Asp	Lys	Arg	Val	Glu	Ser	Lys	Tyr
		210					215					220				
	Gly	Pro	Pro	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Phe	Leu	Gly	Gly	Pro
30	225					230					235					240
	Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser
				245						250					255	
	Arg	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	Gln	Glu	Asp
				260					265					270		
35	Pro	Glu	Val	Gln	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn
			275					280					285			
	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Phe	Asn	Ser	Thr	Tyr	Arg	Val
		290					295					300				
	Val	Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu
	305					310					315					320
40	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Gly	Leu	Pro	Ser	Ser	Ile	Glu	Lys
				325						330					335	
	Thr	Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr
				340					345					350		
	Leu	Pro	Pro	Ser	Gln	Glu	Glu	Met	Thr	Lys	Asn	Gln	Val	Ser	Leu	Thr
45			355					360					365			
	Cys	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu
		370					375					380				
	Ser	Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Val	Leu
	385					390					395					400
50	Asp	Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser	Arg	Leu	Thr	Val	Asp	Lys
				405						410					415	
	Ser	Arg	Trp	Gln	Glu	Gly	Asn	Val	Phe	Ser	Cys	Ser	Val	Met	His	Glu
				420					425					430		
	Ala	Leu	His	Asn	His	Tyr	Thr	Gln	Lys	Ser	Leu	Ser	Leu	Ser	Leu	Gly
			435					440					445			
55	Lys															

<210> 92

<211> 449

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<212> PRT

<213> Artificial Sequence

<220>

5 <223> Candidate 18 Full length heavy chain

<400> 92

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	1				5					10					15	
	Thr	Leu	Ser	Leu	Thr	Cys	Ala	Ile	Ser	Gly	Asp	Ser	Val	Ser	Ser	Asn
				20					25					30		
	Ser	Ala	Ala	Trp	Gly	Trp	Ile	Arg	Gln	Ser	Pro	Gly	Arg	Gly	Leu	Glu
			35					40					45			
15	Trp	Leu	Gly	Ile	Ile	Gln	Lys	Arg	Ser	Lys	Trp	Tyr	Asn	Asn	Tyr	Ala
		50					55					60				
	Val	Ser	Val	Lys	Ser	Arg	Ile	Thr	Ile	Asn	Pro	Asp	Thr	Ser	Lys	Asn

20

25

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35

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45

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55

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	65				70				75				80			
	Gln	Phe	Ser	Leu	Gln	Leu	Asn	Ser	Val	Thr	Pro	Glu	Asp	Thr	Ala	Val
					85					90					95	
5	Tyr	Tyr	Cys	Ala	Arg	Tyr	Ser	Tyr	Pro	Phe	Tyr	Ser	Ile	Asp	Tyr	Trp
				100					105					110		
	Gly	Gln	Gly	Thr	Leu	Val	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro
			115					120					125			
	Ser	Val	Phe	Pro	Leu	Ala	Pro	Cys	Ser	Arg	Ser	Thr	Ser	Glu	Ser	Thr
		130					135					140				
10	Ala	Ala	Leu	Gly	Cys	Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr
	145					150					155				160	
	Val	Ser	Trp	Asn	Ser	Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro
				165					170						175	
	Ala	Val	Leu	Gln	Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr
				180					185					190		
15	Val	Pro	Ser	Ser	Ser	Leu	Gly	Thr	Lys	Thr	Tyr	Thr	Cys	Asn	Val	Asp
		195						200					205			
	His	Lys	Pro	Ser	Asn	Thr	Lys	Val	Asp	Lys	Arg	Val	Glu	Ser	Lys	Tyr
		210				215						220				
20	Gly	Pro	Pro	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Phe	Leu	Gly	Gly	Pro
	225				230						235				240	
	Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser
				245					250					255		
	Arg	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	Gln	Glu	Asp
				260					265					270		
25	Pro	Glu	Val	Gln	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn
		275						280					285			
	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Gln	Phe	Asn	Ser	Thr	Tyr	Arg	Val	
		290				295					300					
	Val	Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu
	305				310					315					320	
30	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Gly	Leu	Pro	Ser	Ser	Ile	Glu	Lys
				325					330					335		
	Thr	Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr
				340				345					350			
35	Leu	Pro	Pro	Ser	Gln	Glu	Glu	Met	Thr	Lys	Asn	Gln	Val	Ser	Leu	Thr
		355						360					365			
	Cys	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu
		370				375					380					
	Ser	Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Val	Leu
	385				390					395					400	
40	Asp	Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser	Arg	Leu	Thr	Val	Asp	Lys
				405					410					415		
	Ser	Arg	Trp	Gln	Glu	Gly	Asn	Val	Phe	Ser	Cys	Ser	Val	Met	His	Glu
				420				425					430			
	Ala	Leu	His	Asn	His	Tyr	Thr	Gln	Lys	Ser	Leu	Ser	Leu	Ser	Leu	Gly
			435				440					445				
45	Lys															

<210> 93

<211> 448

<212> PRT

50 <213> Artificial Sequence

<220>

<223> Candidate 19 Full length heavy chain

55 <400> 93

Gln	Val	Glu	Leu	Val	Gln	Ser	Gly	Ala	Glu	Val	Lys	Lys	Pro	Gly	Glu
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				20					25					30		
	Trp	Val	Gly	Trp	Val	Arg	Gln	Met	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Met
			35					40					45			
5	Gly	Phe	Ile	Asp	Pro	Ser	Asp	Ser	Tyr	Thr	Asn	Tyr	Ala	Pro	Ser	Phe
		50					55					60				
	Gln	Gly	Gln	Val	Thr	Ile	Ser	Ala	Asp	Lys	Ser	Ile	Ser	Thr	Ala	Tyr
	65					70					75					80
	Leu	Gln	Trp	Ser	Ser	Leu	Lys	Ala	Ser	Asp	Thr	Ala	Met	Tyr	Tyr	Cys
10					85					90					95	
	Ala	Arg	Glu	Leu	Tyr	Gln	Gly	Tyr	Met	Asp	Thr	Phe	Asp	Ser	Trp	Gly
				100					105					110		
	Gln	Gly	Thr	Leu	Val	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro	Ser
			115					120					125			
15	Val	Phe	Pro	Leu	Ala	Pro	Cys	Ser	Arg	Ser	Thr	Ser	Glu	Ser	Thr	Ala
		130					135					140				
	Ala	Leu	Gly	Cys	Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val
	145					150					155					160
	Ser	Trp	Asn	Ser	Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro	Ala
					165					170					175	
20	Val	Leu	Gln	Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val
				180					185					190		
	Pro	Ser	Ser	Ser	Leu	Gly	Thr	Lys	Thr	Tyr	Thr	Cys	Asn	Val	Asp	His
			195					200					205			
	Lys	Pro	Ser	Asn	Thr	Lys	Val	Asp	Lys	Arg	Val	Glu	Ser	Lys	Tyr	Gly
25		210					215					220				
	Pro	Pro	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Phe	Leu	Gly	Gly	Pro	Ser
						230					235					240
	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser	Arg
				245						250					255	
30	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	Gln	Glu	Asp	Pro
				260					265					270		
	Glu	Val	Gln	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn	Ala
			275					280					285			
	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Phe	Asn	Ser	Thr	Tyr	Arg	Val	Val
		290					295					300				
35	Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu	Tyr
		305				310					315					320
	Lys	Cys	Lys	Val	Ser	Asn	Lys	Gly	Leu	Pro	Ser	Ser	Ile	Glu	Lys	Thr
					325					330					335	
	Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr	Leu
40				340					345					350		
	Pro	Pro	Ser	Gln	Glu	Glu	Met	Thr	Lys	Asn	Gln	Val	Ser	Leu	Thr	Cys
			355					360					365			
	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu	Ser
						375						380				
45	Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Val	Leu	Asp
		385				390					395					400
	Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser	Arg	Leu	Thr	Val	Asp	Lys	Ser
					405					410					415	
	Arg	Trp	Gln	Glu	Gly	Asn	Val	Phe	Ser	Cys	Ser	Val	Met	His	Glu	Ala
				420					425					430		
50	Leu	His	Asn	His	Tyr	Thr	Gln	Lys	Ser	Leu	Ser	Leu	Ser	Leu	Gly	Lys
			435					440					445			

<210> 94

<211> 446

55 <212> PRT

<213> Artificial Sequence

<220>

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<223> Candidate 1 Full length heavy chain

<400> 94

5	Gln	Val	Glu	Leu	Val	Gln	Ser	Gly	Ala	Glu	Val	Lys	Lys	Pro	Gly	Glu
	1				5					10					15	
	Ser	Leu	Lys	Ile	Ser	Cys	Lys	Gly	Ser	Gly	Tyr	Ser	Phe	Thr	Asp	Asn
				20					25					30		
10	Trp	Ile	Ser	Trp	Val	Arg	Gln	Ala	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Met
			35					40					45			
	Gly	Val	Ile	Asp	Pro	Ser	Asp	Ser	Tyr	Thr	Asn	Tyr	Ala	Pro	Ser	Phe
		50					55					60				
	Gln	Gly	Gln	Val	Thr	Ile	Ser	Ala	Asp	Lys	Ser	Ile	Ser	Thr	Ala	Tyr
	65					70					75					80
15	Leu	Gln	Trp	Ser	Ser	Leu	Lys	Ala	Ser	Asp	Thr	Ala	Met	Tyr	Tyr	Cys
					85					90					95	
	Ala	Arg	Glu	Trp	Gly	Ile	Gly	Gly	Met	Val	Asp	Ile	Trp	Gly	Gln	Gly
				100					105					110		
	Thr	Leu	Val	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro	Ser	Val	Phe
				115					120					125		
20	Pro	Leu	Ala	Pro	Cys	Ser	Arg	Ser	Thr	Ser	Glu	Ser	Thr	Ala	Ala	Leu
		130					135						140			
	Gly	Cys	Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val	Ser	Trp
	145					150					155					160
	Asn	Ser	Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro	Ala	Val	Leu
25					165					170					175	
	Gln	Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val	Pro	Ser
				180					185					190		
	Ser	Ser	Leu	Gly	Thr	Lys	Thr	Tyr	Thr	Cys	Asn	Val	Asp	His	Lys	Pro
			195					200					205			
30	Ser	Asn	Thr	Lys	Val	Asp	Lys	Arg	Val	Glu	Ser	Lys	Tyr	Gly	Pro	Pro
		210					215						220			
	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Phe	Leu	Gly	Gly	Pro	Ser	Val	Phe
	225					230					235					240
	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser	Arg	Thr	Pro
					245					250					255	
35	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	Gln	Glu	Asp	Pro	Glu	Val
				260					265					270		
	Gln	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn	Ala	Lys	Thr
			275					280					285			
	Lys	Pro	Arg	Glu	Glu	Gln	Phe	Asn	Ser	Thr	Tyr	Arg	Val	Val	Ser	Val
40				290			295						300			
	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu	Tyr	Lys	Cys
	305					310					315					320
	Lys	Val	Ser	Asn	Lys	Gly	Leu	Pro	Ser	Ser	Ile	Glu	Lys	Thr	Ile	Ser
					325					330					335	
45	Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr	Leu	Pro	Pro
				340					345					350		
	Ser	Gln	Glu	Met	Thr	Lys	Asn	Gln	Val	Ser	Leu	Thr	Cys	Leu	Val	
			355				360					365				
	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu	Ser	Asn	Gly
		370					375					380				
50	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Val	Leu	Asp	Ser	Asp
	385					390					395					400
	Gly	Ser	Phe	Phe	Leu	Tyr	Ser	Arg	Leu	Thr	Val	Asp	Lys	Ser	Arg	Trp
					405					410					415	
	Gln	Glu	Gly	Asn	Val	Phe	Ser	Cys	Ser	Val	Met	His	Glu	Ala	Leu	His
				420					425					430		
55	Asn	His	Tyr	Thr	Gln	Lys	Ser	Leu	Ser	Leu	Ser	Leu	Gly	Lys		
			435					440					445			

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<210> 95
<211> 443
<212> PRT
<213> Artificial Sequence

5

<220>
<223> Candidate 2 Full length heavy chain

10

<400> 95

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	Gln	Val	Glu	Leu	Val	Gln	Ser	Gly	Ala	Glu	Val	Lys	Lys	Pro	Gly	Glu
	1				5					10					15	
	Ser	Leu	Lys	Ile	Ser	Cys	Lys	Gly	Ser	Gly	Tyr	Ser	Phe	Asn	Asn	Tyr
				20					25					30		
5	Trp	Ile	Gly	Trp	Val	Arg	Gln	Met	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Met
			35					40					45			
	Gly	Ile	Ile	Asp	Pro	Gln	Asp	Ser	Trp	Thr	Asn	Tyr	Ala	Pro	Ser	Phe
		50					55					60				
10	Gln	Gly	Gln	Val	Thr	Ile	Ser	Ala	Asp	Lys	Ser	Ile	Ser	Thr	Ala	Tyr
	65					70					75					80
	Leu	Gln	Trp	Ser	Ser	Leu	Lys	Ala	Ser	Asp	Thr	Ala	Met	Tyr	Tyr	Cys
					85					90					95	
	Ala	Arg	Asn	Ile	Tyr	Glu	Phe	Asp	Tyr	Trp	Gly	Gln	Gly	Thr	Leu	Val
				100					105					110		
15	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro	Ser	Val	Phe	Pro	Leu	Ala
			115					120					125			
	Pro	Cys	Ser	Arg	Ser	Thr	Ser	Glu	Ser	Thr	Ala	Ala	Leu	Gly	Cys	Leu
		130					135					140				
	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val	Ser	Trp	Asn	Ser	Gly
	145					150					155					160
20	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro	Ala	Val	Leu	Gln	Ser	Ser
					165					170					175	
	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val	Pro	Ser	Ser	Ser	Leu
				180					185					190		
25	Gly	Thr	Lys	Thr	Tyr	Thr	Cys	Asn	Val	Asp	His	Lys	Pro	Ser	Asn	Thr
			195					200					205			
	Lys	Val	Asp	Lys	Arg	Val	Glu	Ser	Lys	Tyr	Gly	Pro	Pro	Cys	Pro	Pro
		210					215					220				
	Cys	Pro	Ala	Pro	Glu	Phe	Leu	Gly	Gly	Pro	Ser	Val	Phe	Leu	Phe	Pro
	225					230					235					240
30	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser	Arg	Thr	Pro	Glu	Val	Thr
					245					250					255	
	Cys	Val	Val	Val	Asp	Val	Ser	Gln	Glu	Asp	Pro	Glu	Val	Gln	Phe	Asn
				260					265					270		
	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn	Ala	Lys	Thr	Lys	Pro	Arg
			275					280						285		
35	Glu	Glu	Gln	Phe	Asn	Ser	Thr	Tyr	Arg	Val	Val	Ser	Val	Leu	Thr	Val
		290					295					300				
	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu	Tyr	Lys	Cys	Lys	Val	Ser
	305					310					315					320
	Asn	Lys	Gly	Leu	Pro	Ser	Ser	Ile	Glu	Lys	Thr	Ile	Ser	Lys	Ala	Lys
					325					330					335	
40	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr	Leu	Pro	Pro	Ser	Gln	Glu
				340					345					350		
	Glu	Met	Thr	Lys	Asn	Gln	Val	Ser	Leu	Thr	Cys	Leu	Val	Lys	Gly	Phe
			355					360					365			
45	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu	Ser	Asn	Gly	Gln	Pro	Glu
		370					375					380				
	Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Val	Leu	Asp	Ser	Asp	Gly	Ser	Phe
	385					390					395					400
	Phe	Leu	Tyr	Ser	Arg	Leu	Thr	Val	Asp	Lys	Ser	Arg	Trp	Gln	Glu	Gly
					405					410					415	
50	Asn	Val	Phe	Ser	Cys	Ser	Val	Met	His	Glu	Ala	Leu	His	Asn	His	Tyr
				420					425					430		
	Thr	Gln	Lys	Ser	Leu	Ser	Leu	Ser	Leu	Gly	Lys					

435

440

<210> 96
<211> 449

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<212> PRT

<213> Artificial Sequence

<220>

5 <223> Candidate 3 Full length heavy chain

<400> 96

10	Gln Val Glu Leu Gln Gln Ser Gly Pro Gly Leu Val Lys Pro Ser Gln	1 5 10 15
	Thr Leu Ser Leu Thr Cys Ala Ile Ser Gly Asp Ser Val Ser Thr Arg	20 25 30
	Ser Ala Ala Trp Gly Trp Ile Arg Gln Ser Pro Gly Arg Gly Leu Glu	35 40 45
15	Trp Leu Gly Arg Ile His Arg Arg Ser Lys Trp Tyr Asn Asp Tyr Ala	50 55 60
	Val Ser Val Lys Ser Arg Ile Thr Ile Asn Pro Asp Thr Ser Lys Asn	65 70 75 80
	Gln Phe Ser Leu Gln Leu Asn Ser Val Thr Pro Glu Asp Thr Ala Val	85 90 95
20	Tyr Tyr Cys Ala Arg His Thr Tyr Pro Tyr Leu Ser Phe Asp Val Trp	100 105 110
	Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro	115 120 125
25	Ser Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr	130 135 140
	Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr	145 150 155 160
	Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro	165 170 175
30	Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr	180 185 190
	Val Pro Ser Ser Ser Leu Gly Thr Lys Thr Tyr Thr Cys Asn Val Asp	195 200 205
	His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys Tyr	210 215 220
35	Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe Leu Gly Gly Pro	225 230 235 240
	Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser	245 250 255
40	Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp	260 265 270
	Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn	275 280 285
	Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val	290 295 300
45	Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu	305 310 315 320
	Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys	325 330 335
	Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr	340 345 350
50	Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr	355 360 365
	Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu	370 375 380
55	Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu	385 390 395 400

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	Asp	Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser	Arg	Leu	Thr	Val	Asp	Lys
					405					410					415	
	Ser	Arg	Trp	Gln	Glu	Gly	Asn	Val	Phe	Ser	Cys	Ser	Val	Met	His	Glu
				420					425					430		
5	Ala	Leu	His	Asn	His	Tyr	Thr	Gln	Lys	Ser	Leu	Ser	Leu	Ser	Leu	Gly
			435					440					445			
	Lys															

<210> 97
 10 <211> 449
 <212> PRT
 <213> Artificial Sequence

<220>
 15 <223> Candidate 4 Full length heavy chain

<400> 97

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	Gln	Val	Glu	Leu	Gln	Gln	Ser	Gly	Pro	Gly	Leu	Val	Lys	Pro	Ser	Gln
	1				5					10					15	
	Thr	Leu	Ser	Leu	Thr	Cys	Ala	Ile	Ser	Gly	Asp	Ser	Val	Ser	Thr	Arg
5				20					25					30		
	Ser	Ala	Ala	Trp	Gly	Trp	Ile	Arg	Gln	Ser	Pro	Gly	Arg	Gly	Leu	Glu
		35						40					45			
	Trp	Leu	Gly	Lys	Ile	Ser	Tyr	Arg	Ser	Arg	Trp	Tyr	Asn	Asp	Tyr	Ala
		50					55					60				
10	Val	Ser	Val	Lys	Ser	Arg	Ile	Thr	Ile	Asn	Pro	Asp	Thr	Ser	Lys	Asn
	65					70					75					80
	Gln	Phe	Ser	Leu	Gln	Leu	Asn	Ser	Val	Thr	Pro	Glu	Asp	Thr	Ala	Val
					85					90					95	
	Tyr	Tyr	Cys	Ala	Arg	His	Thr	Tyr	Pro	Tyr	Leu	Ser	Phe	Asp	Val	Trp
				100					105					110		
15	Gly	Gln	Gly	Thr	Leu	Val	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro
			115					120					125			
	Ser	Val	Phe	Pro	Leu	Ala	Pro	Cys	Ser	Arg	Ser	Thr	Ser	Glu	Ser	Thr
		130					135					140				
	Ala	Ala	Leu	Gly	Cys	Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr
20		145				150					155					160
	Val	Ser	Trp	Asn	Ser	Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro
				165						170					175	
	Ala	Val	Leu	Gln	Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr
				180				185						190		
25	Val	Pro	Ser	Ser	Ser	Leu	Gly	Thr	Lys	Thr	Tyr	Thr	Cys	Asn	Val	Asp
			195					200					205			
	His	Lys	Pro	Ser	Asn	Thr	Lys	Val	Asp	Lys	Arg	Val	Glu	Ser	Lys	Tyr
		210					215					220				
	Gly	Pro	Pro	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Phe	Leu	Gly	Gly	Pro
		225				230					235					240
30	Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser
				245						250					255	
	Arg	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	Gln	Glu	Asp
				260					265					270		
	Pro	Glu	Val	Gln	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn
			275					280					285			
35	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Phe	Asn	Ser	Thr	Tyr	Arg	Val
		290					295					300				
	Val	Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu
		305				310					315					320
40	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Gly	Leu	Pro	Ser	Ser	Ile	Glu	Lys
				325						330					335	
	Thr	Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr
				340					345					350		
45	Leu	Pro	Pro	Ser	Gln	Glu	Glu	Met	Thr	Lys	Asn	Gln	Val	Ser	Leu	Thr
			355					360					365			
	Cys	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu
		370					375					380				
	Ser	Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Val	Leu
		385				390					395					400
50	Asp	Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser	Arg	Leu	Thr	Val	Asp	Lys
				405						410					415	
	Ser	Arg	Trp	Gln	Glu	Gly	Asn	Val	Phe	Ser	Cys	Ser	Val	Met	His	Glu
			420						425					430		
	Ala	Leu	His	Asn	His	Tyr	Thr	Gln	Lys	Ser	Leu	Ser	Leu	Ser	Leu	Gly
55			435					440					445			
	Lys															

<210> 98

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<211> 449
<212> PRT
<213> Artificial Sequence

5 <220>
<223> Candidate 5,6,7 Full length heavy chain

<400> 98

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10      Gln Val Glu Leu Gln Gln Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
        1          5          10          15
        Thr Leu Ser Leu Thr Cys Ala Ile Ser Gly Asp Ser Val Ser Thr Arg
          20          25          30
        Ser Ala Ala Trp Gly Trp Ile Arg Gln Ser Pro Gly Arg Gly Leu Glu
15      35          40          45
        Trp Leu Gly Arg Ile Tyr Met Arg Ser Lys Trp Tyr Asn Asp Tyr Ala
        50          55          60
        Val Ser Val Lys Ser Arg Ile Thr Ile Asn Pro Asp Thr Ser Lys Asn
        65          70          75          80
20      Gln Phe Ser Leu Gln Leu Asn Ser Val Thr Pro Glu Asp Thr Ala Val
          85          90          95
        Tyr Tyr Cys Ala Arg His Thr Tyr Pro Tyr Leu Ser Phe Asp Val Trp
          100          105          110
        Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro
          115          120          125
25      Ser Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr
        130          135          140
        Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr
        145          150          155          160
        Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro
30      165          170          175
        Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr
          180          185          190
        Val Pro Ser Ser Ser Leu Gly Thr Lys Thr Tyr Thr Cys Asn Val Asp
          195          200          205
35      His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys Tyr
        210          215          220
        Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe Leu Gly Gly Pro
        225          230          235          240
        Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
          245          250          255
40      Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp
          260          265          270
        Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
          275          280          285

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	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Phe	Asn	Ser	Thr	Tyr	Arg	Val
	290						295				300					
	Val	Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu
	305					310				315						320
5	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Gly	Leu	Pro	Ser	Ser	Ile	Glu	Lys
				325						330					335	
	Thr	Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr
				340					345					350		
	Leu	Pro	Pro	Ser	Gln	Glu	Glu	Met	Thr	Lys	Asn	Gln	Val	Ser	Leu	Thr
10			355					360					365			
	Cys	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu
	370						375				380					
	Ser	Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Val	Leu
	385					390					395					400
15	Asp	Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser	Arg	Leu	Thr	Val	Asp	Lys
				405						410					415	
	Ser	Arg	Trp	Gln	Glu	Gly	Asn	Val	Phe	Ser	Cys	Ser	Val	Met	His	Glu
				420					425					430		
	Ala	Leu	His	Asn	His	Tyr	Thr	Gln	Lys	Ser	Leu	Ser	Leu	Ser	Leu	Gly
			435					440					445			
20	Lys															

<210> 99

<211> 449

<212> PRT

25 <213> Artificial Sequence

<220>

<223> Candidate 8 Full length heavy chain

30 <400> 99

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	Gln	Val	Glu	Leu	Gln	Gln	Ser	Gly	Pro	Gly	Leu	Val	Lys	Pro	Ser	Gln
	1				5					10					15	
	Thr	Leu	Ser	Leu	Thr	Cys	Ala	Ile	Ser	Gly	Asp	Ser	Val	Ser	Ser	Asn
5				20					25					30		
	Ser	Ala	Ala	Trp	Gly	Trp	Ile	Arg	Gln	Ser	Pro	Gly	Arg	Gly	Leu	Glu
		35						40					45			
	Trp	Leu	Gly	Ile	Ile	Gln	Thr	Arg	Ser	Lys	Trp	Tyr	Asn	Asp	Tyr	Ala
		50					55					60				
10	Val	Ser	Val	Lys	Ser	Arg	Ile	Thr	Ile	Asn	Pro	Asp	Thr	Ser	Lys	Asn
	65					70					75					80
	Gln	Phe	Ser	Leu	Gln	Leu	Asn	Ser	Val	Thr	Pro	Glu	Asp	Thr	Ala	Val
					85					90					95	
	Tyr	Tyr	Cys	Ala	Arg	Tyr	Ser	Tyr	Pro	Phe	Tyr	Ser	Ile	Asp	Tyr	Trp
				100					105					110		
15	Gly	Gln	Gly	Thr	Leu	Val	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro
			115					120					125			
	Ser	Val	Phe	Pro	Leu	Ala	Pro	Cys	Ser	Arg	Ser	Thr	Ser	Glu	Ser	Thr
		130					135					140				
	Ala	Ala	Leu	Gly	Cys	Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr
20	145					150					155					160
	Val	Ser	Trp	Asn	Ser	Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro
				165						170					175	
	Ala	Val	Leu	Gln	Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr
				180				185						190		
25	Val	Pro	Ser	Ser	Ser	Leu	Gly	Thr	Lys	Thr	Tyr	Thr	Cys	Asn	Val	Asp
			195					200					205			
	His	Lys	Pro	Ser	Asn	Thr	Lys	Val	Asp	Lys	Arg	Val	Glu	Ser	Lys	Tyr
		210					215					220				
	Gly	Pro	Pro	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Phe	Leu	Gly	Gly	Pro
30																
	225					230				235						240
	Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser
					245					250					255	
	Arg	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	Gln	Glu	Asp
35				260					265					270		
	Pro	Glu	Val	Gln	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn
			275					280					285			
	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Phe	Asn	Ser	Thr	Tyr	Arg	Val
		290					295					300				
40	Val	Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu
	305					310					315					320
	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Gly	Leu	Pro	Ser	Ser	Ile	Glu	Lys
					325					330					335	
	Thr	Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr
				340					345					350		
45	Leu	Pro	Pro	Ser	Gln	Glu	Glu	Met	Thr	Lys	Asn	Gln	Val	Ser	Leu	Thr
			355					360					365			
	Cys	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu
		370					375					380				
	Ser	Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Val	Leu
50	385					390					395					400
	Asp	Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser	Arg	Leu	Thr	Val	Asp	Lys
					405					410					415	
	Ser	Arg	Trp	Gln	Glu	Gly	Asn	Val	Phe	Ser	Cys	Ser	Val	Met	His	Glu
				420					425					430		
55	Ala	Leu	His	Asn	His	Tyr	Thr	Gln	Lys	Ser	Leu	Ser	Leu	Ser	Leu	Gly
			435					440					445			
	Lys															

<210> 100

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<211> 449
 <212> PRT
 <213> Artificial Sequence

5 <220>
 <223> Candidate 9 Full length heavy chain

<400> 100

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10      Gln Val Glu Leu Gln Gln Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
        1          5          10          15
        Thr Leu Ser Leu Thr Cys Ala Ile Ser Gly Asp Ser Val Ser Ser Asn
          20          25          30
        Ser Ala Ala Trp Gly Trp Ile Arg Gln Ser Pro Gly Arg Gly Leu Glu
15      35          40          45
        Trp Leu Gly Ile Ile Gln Ile Arg Ser Lys Trp Tyr Asn Asp Tyr Ala
        50          55          60
        Leu Ser Val Lys Ser Arg Ile Thr Ile Asn Pro Asp Thr Ser Lys Asn
        65          70          75          80
20      Gln Phe Ser Leu Gln Leu Asn Ser Val Thr Pro Glu Asp Thr Ala Val
          85          90          95
        Tyr Tyr Cys Ala Arg Tyr Ser Tyr Pro Phe Tyr Ser Ile Asp Tyr Trp
          100          105          110
        Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro
          115          120          125
25      Ser Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr
          130          135          140
        Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr
        145          150          155          160
30      Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro
          165          170          175
  
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	Ala	Val	Leu	Gln	Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr
				180					185					190		
	Val	Pro	Ser	Ser	Ser	Leu	Gly	Thr	Lys	Thr	Tyr	Thr	Cys	Asn	Val	Asp
			195					200					205			
5	His	Lys	Pro	Ser	Asn	Thr	Lys	Val	Asp	Lys	Arg	Val	Glu	Ser	Lys	Tyr
		210					215					220				
	Gly	Pro	Pro	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Phe	Leu	Gly	Gly	Pro
		225				230					235					240
	Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser
10				245						250					255	
	Arg	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	Gln	Glu	Asp
			260					265						270		
	Pro	Glu	Val	Gln	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn
			275					280					285			
15	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Phe	Asn	Ser	Thr	Tyr	Arg	Val
		290					295					300				
	Val	Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu
		305				310					315					320
	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Gly	Leu	Pro	Ser	Ser	Ile	Glu	Lys
				325						330					335	
20	Thr	Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr
				340					345					350		
	Leu	Pro	Pro	Ser	Gln	Glu	Glu	Met	Thr	Lys	Asn	Gln	Val	Ser	Leu	Thr
			355					360					365			
	Cys	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu
25			370				375					380				
	Ser	Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Val	Leu
		385				390					395					400
	Asp	Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser	Arg	Leu	Thr	Val	Asp	Lys
				405						410					415	
30	Ser	Arg	Trp	Gln	Glu	Gly	Asn	Val	Phe	Ser	Cys	Ser	Val	Met	His	Glu
			420						425					430		
	Ala	Leu	His	Asn	His	Tyr	Thr	Gln	Lys	Ser	Leu	Ser	Leu	Ser	Leu	Gly
			435					440					445			

Lys

35 <210> 101
 <211> 449
 <212> PRT
 <213> Artificial Sequence

40 <220>
 <223> Candidate 10,11, 12 Full length heavy chain

<400> 101

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	Gln	Val	Glu	Leu	Gln	Gln	Ser	Gly	Pro	Gly	Leu	Val	Lys	Pro	Ser	Gln
	1				5					10					15	
	Thr	Leu	Ser	Leu	Thr	Cys	Ala	Ile	Ser	Gly	Asp	Ser	Val	Ser	Ser	Asn
5				20					25					30		
	Ser	Ala	Ala	Trp	Gly	Trp	Ile	Arg	Gln	Ser	Pro	Gly	Arg	Gly	Leu	Glu
		35						40					45			
	Trp	Leu	Gly	Ile	Ile	Gln	Lys	Arg	Ser	Lys	Trp	Tyr	Asn	Asn	Tyr	Ala
		50					55					60				
10	Val	Ser	Val	Lys	Ser	Arg	Ile	Thr	Ile	Asn	Pro	Asp	Thr	Ser	Lys	Asn
	65					70					75					80
	Gln	Phe	Ser	Leu	Gln	Leu	Asn	Ser	Val	Thr	Pro	Glu	Asp	Thr	Ala	Val
					85					90					95	
	Tyr	Tyr	Cys	Ala	Arg	Tyr	Ser	Tyr	Pro	Phe	Tyr	Ser	Ile	Asp	Tyr	Trp
			100						105					110		
15	Gly	Gln	Gly	Thr	Leu	Val	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro
				115				120					125			
	Ser	Val	Phe	Pro	Leu	Ala	Pro	Cys	Ser	Arg	Ser	Thr	Ser	Glu	Ser	Thr
20		130					135					140				
	Ala	Ala	Leu	Gly	Cys	Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr
	145					150					155					160
	Val	Ser	Trp	Asn	Ser	Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro
				165						170					175	
25	Ala	Val	Leu	Gln	Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr
				180					185					190		
	Val	Pro	Ser	Ser	Ser	Leu	Gly	Thr	Lys	Thr	Tyr	Thr	Cys	Asn	Val	Asp
		195						200					205			
	His	Lys	Pro	Ser	Asn	Thr	Lys	Val	Asp	Lys	Arg	Val	Glu	Ser	Lys	Tyr
		210					215					220				
30	Gly	Pro	Pro	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Phe	Leu	Gly	Gly	Pro
	225					230					235					240
	Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser
				245						250					255	
	Arg	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	Gln	Glu	Asp
35				260					265					270		
	Pro	Glu	Val	Gln	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn
		275						280					285			
	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Phe	Asn	Ser	Thr	Tyr	Arg	Val
		290					295					300				
40	Val	Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu
	305					310					315					320
	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Gly	Leu	Pro	Ser	Ser	Ile	Glu	Lys
				325						330					335	
	Thr	Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr
				340					345					350		
45	Leu	Pro	Pro	Ser	Gln	Glu	Glu	Met	Thr	Lys	Asn	Gln	Val	Ser	Leu	Thr
			355					360					365			
	Cys	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu
		370					375					380				
	Ser	Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Val	Leu
50	385					390					395					400
	Asp	Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser	Arg	Leu	Thr	Val	Asp	Lys
				405						410					415	
	Ser	Arg	Trp	Gln	Glu	Gly	Asn	Val	Phe	Ser	Cys	Ser	Val	Met	His	Glu
				420					425					430		
55	Ala	Leu	His	Asn	His	Tyr	Thr	Gln	Lys	Ser	Leu	Ser	Leu	Ser	Leu	Gly
			435					440					445			
	Lys															

<210> 102

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<211> 448
 <212> PRT
 <213> Artificial Sequence

5 <220>
 <223> Candidate 13, 14, 15, 15-7, 15-8 Full length heavy chain

<400> 102

10 Gln Val Glu Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
 1 5 10 15
 Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Asn Tyr
 20 25 30
 Trp Val Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
 15 35 40 45
 Gly Phe Ile Asp Pro Ser Asp Ser Tyr Thr Asn Tyr Ala Pro Ser Phe
 50 55 60

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	Gln	Gly	Gln	Val	Thr	Ile	Ser	Ala	Asp	Lys	Ser	Ile	Ser	Thr	Ala	Tyr
	65					70					75					80
	Leu	Gln	Trp	Ser	Ser	Leu	Lys	Ala	Ser	Asp	Thr	Ala	Met	Tyr	Tyr	Cys
				85						90					95	
5	Ala	Arg	Glu	Leu	Tyr	Gln	Gly	Tyr	Met	Asp	Thr	Phe	Asp	Ser	Trp	Gly
				100					105					110		
	Gln	Gly	Thr	Leu	Val	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro	Ser
			115					120					125			
	Val	Phe	Pro	Leu	Ala	Pro	Cys	Ser	Arg	Ser	Thr	Ser	Glu	Ser	Thr	Ala
10		130					135					140				
	Ala	Leu	Gly	Cys	Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val
	145					150					155					160
	Ser	Trp	Asn	Ser	Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro	Ala
				165						170					175	
15	Val	Leu	Gln	Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val
				180					185					190		
	Pro	Ser	Ser	Ser	Leu	Gly	Thr	Lys	Thr	Tyr	Thr	Cys	Asn	Val	Asp	His
			195					200					205			
	Lys	Pro	Ser	Asn	Thr	Lys	Val	Asp	Lys	Arg	Val	Glu	Ser	Lys	Tyr	Gly
		210					215					220				
20	Pro	Pro	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Phe	Leu	Gly	Gly	Pro	Ser
	225					230					235					240
	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser	Arg
				245						250					255	
25	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	Gln	Glu	Asp	Pro
				260						265					270	
	Glu	Val	Gln	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn	Ala
			275						280					285		
	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Phe	Asn	Ser	Thr	Tyr	Arg	Val	Val
		290					295					300				
30	Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu	Tyr
	305					310					315					320
	Lys	Cys	Lys	Val	Ser	Asn	Lys	Gly	Leu	Pro	Ser	Ser	Ile	Glu	Lys	Thr
				325						330					335	
	Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr	Leu
				340					345					350		
35	Pro	Pro	Ser	Gln	Glu	Glu	Met	Thr	Lys	Asn	Gln	Val	Ser	Leu	Thr	Cys
			355					360						365		
	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu	Ser
		370					375						380			
40	Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Val	Leu	Asp
	385					390						395				400
	Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser	Arg	Leu	Thr	Val	Asp	Lys	Ser
				405						410					415	
	Arg	Trp	Gln	Glu	Gly	Asn	Val	Phe	Ser	Cys	Ser	Val	Met	His	Glu	Ala
			420						425					430		
45	Leu	His	Asn	His	Tyr	Thr	Gln	Lys	Ser	Leu	Ser	Leu	Ser	Leu	Gly	Lys
			435					440						445		

<210> 103

<211> 19

<212> PRT

50 <213> Artificial Sequence

<220>

<223> N-terminal leader sequence for expressing heavy chains

55 <400> 103

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Met Ala Trp Val Trp Thr Leu Leu Phe Leu Met Ala Ala Ala Gln Ser
 1 5 10 15
 Ile Gln Ala

5 <210> 104
 <211> 1401
 <212> DNA
 <213> Artificial Sequence

10 <220>
 <223> Full length IgG4 Heavy chains of Candidate **15EVQ**
 with leader sequence

15 <400> 104

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 gtgcagctgg tgcagagcgg cgccgaggtg aagaagcccg gcgagagcct gaagatcagc 120
 tgcaaggggca gcggctacag cttcaccaac tactgggtgg gctgggtgcg ccagatgccc 180
 20 ggcaaggggcc tggagtggat gggcttcac gacccagcg acagctacac caactacgcg 240
 cctagcttcc agggccaggt gaccatcagc gccgacaaga gcatcagcac cgcctacctg 300
 cagtggagca gcctgaaggc cagcgacacc gccatgtact actgcgcccg cgagctgtac 360
 cagggctaca tggacacgtt cgacagctgg ggccagggca ccctggtgac cgtgagcagc 420
 gcttccacca agggcccatc cgtcttcccc ctggcgccct gctccaggag cacctccgag 480
 agcacagccg ccctgggctg cctggtcaag gactacttcc ccgaaccggg gacggtgtcg 540
 25 tggaaactcag gcgccctgac cagcggcgtg cacaccttcc cggctgtcct acagtccctca 600
 ggactctact ccctcagcag cgtggtgacc gtgccctcca gcagcttggg cagcaaaacc 660
 tacacctgca acgtagatca caagcccagc aacaccaagg tggacaagag agttgagtcc 720
 aaatatgggtc ccccatgccc accatgcccga gcacctgagg ccgccggggg accatcagtc 780
 ttctgttcc ccccaaaaacc caaggacact ctcatgatct cccggacccc tgaggtcacg 840
 30 tgcgtggtgg tggacgtgag ccaggaagac cccgaggtcc agttcaactg gtacgtggat 900
 ggcgtggagg tgcataatgc caagacaaag ccgcgggagg agcagttcaa cagcacgtac 960
 cgtgtggtca gcgtcctcac cgtcctgcac caggactggc tgaacggcaa ggagtacaag 1020
 tgcaagggtct ccaacaaagg cctcccgtcc tccatcgaga aaaccatctc caaagccaaa 1080
 gggcagcccc gagagccaca ggtgtacacc ctgcccccat cccaggagga gatgaccaag 1140
 aaccagggtca gcctgacctg cctggtcaaa ggcttctacc ccagcgacat cgccgtggag 1200
 35 tgggagagca atgggcagcc ggagaacaac tacaagacca cgcctcccgt gctggactcc 1260
 gacggctcct tcttctctca cagcaggcta accgtggaca agagcagggt gcaggagggg 1320
 aatgtcttct catgctccgt gatgcatgag gctctgcaca accactacac acagaagagc 1380
 ctctccctgt ctctgggtaa a 1401

40 <210> 105
 <211> 1344
 <212> DNA
 <213> Artificial Sequence

45 <220>
 <223> IgG4 Heavy chains of Candidate **15EVQ** without
 leader sequence

50 <400> 105

55

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gaggtgcagc tgggtgcagag cggcgccgag gtgaagaagc ccggcgagag cctgaagatc 60
 agctgcaagg gcagcggcta cagcttcacc aactactggg tgggctgggt gcgccagatg 120
 cccggcaagg gcctggagtg gatgggcttc atcgacccca gcgacagcta caccaactac 180
 5 gcgcctagct tccagggcca ggtgaccatc agcgccgaca agagcatcag caccgcctac 240
 ctgcagtggg gcagcctgaa ggccagcgac accgccatgt actactgcgc ccgcgagctg 300
 taccagggct acatggacac gttcgacagc tggggccagg gcaccctggg gaccgtgagc 360
 agcgcttcca ccaagggccc atccgtcttc cccctggcgc cctgctccag gagcacctcc 420
 gagagcacag ccgccctggg ctgcctggtc aaggactact tccccgaacc ggtgacgggtg 480
 10 tcgtggaact caggcgccct gaccagcggc gtgcacacct tcccggctgt cctacagtcc 540
 tcaggactct actccctcag cagcgtgggt accgtgccct ccagcagctt gggcacgaaa 600
 acctacacct gcaacgtaga tcacaagccc agcaacacca aggtggacaa gagagttgag 660
 tccaaatatg gtcccccatg cccaccatgc ccagcacctg aggccgccgg gggaccatca 720
 gtcttcctgt tcccccaaa acccaaggac actctcatga tctcccggac ccctgagggtc 780
 acgtgcgtgg tgggtggacgt gagccaggaa gaccccgagg tccagttcaa ctggtacgtg 840
 15 gatggcgtgg aggtgcataa tgccaagaca aagccgcggg aggagcagtt caacagcacg 900

taccgtgtgg tcagcgtcct caccgtcctg caccaggact ggctgaacgg caaggagtac 960
 aagtgcaagg tctccaacaa aggcctcccg tcctccatcg agaaaaccat ctccaaagcc 1020
 20 aaagggcagc cccgagagcc acagggtgac accctgcccc catcccagga ggagatgacc 1080
 agaaccagg tcagcctgac ctgcctggtc aaaggcttct accccagcga catcgccgtg 1140
 gagtgggaga gcaatgggca gccggagAAC aactacaaga ccacgcctcc cgtgctggac 1200
 tccgacggct ccttcttcct ctacagcagg ctaaccgtgg acaagagcag gtggcaggag 1260
 gggaatgtct tctcatgctc cgtgatgcat gaggctctgc acaaccacta cacacagaag 1320
 agcctctccc tgtctctggg taaa 1344

<210> 106
 <211> 20
 <212> PRT
 <213> Artificial Sequence
 30
 <220>
 <223> N-termina leader sequence for expressing light chains
 <400> 106

35
 Met Gly Val Pro Thr Gln Val Leu Gly Leu Leu Leu Leu Trp Leu Thr
 1 5 10 15
 Asp Ala Arg Cys
 20

40
 <210> 107
 <211> 702
 <212> DNA
 <213> Artificial Sequence

45
 <220>
 <223> Full length light chain of Candidate 15 with
 leader sequence

50
 <400> 107

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    atgggtgtgc caactcaggt attaggatta ctgctgctgt ggcttacaga tgcaagatgt 60
    gacatccaga tgaccagag cccagcagc ctgagcgcca gcgtgggcga ccgcgtgacc 120
    atcacctgcc gcgccagcca gagcatcggc ctgtacctgg cctggtacca gcagaagccc 180
5    ggcaaggccc ccaagctgct gatctacgcc gccagcagcc tgcagagcgg cgtgcccagc 240
    cgcttcagcg gcagcggcag cggcaccgac ttcacctga ccatcagcag cctgcagccc 300
    gaggacttcg ccacctacta ctgccagcag ggcaacaccc tgagctacac cttcggccag 360
    ggcaccaagg tggagatcaa gcgtacggtg gctgcacccat ctgtcttcat cttcccgcc 420
    tctgatgagc agttgaaatc tggaactgcc tctgttgtgt gcctgctgaa taacttctat 480
    cccagagagg ccaaagtaca gtggaaggtg gataacgccc tccaatcggg taactcccag 540
10    gagagtgtca cagagcagga cagcaaggac agcacctaca gcctcagcag caccctgacg 600
    ctgagcaaag cagactacga gaaacacaaa gtctacgcct gcgaagtcac ccatcagggc 660
    ctgagctcgc ccgtcacaaa gagcttcaac aggggagagt gt 702

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<210> 108
 <211> 642
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Light chain of Candidate 15 without leader
 sequence (starts DIQ)

<400> 108

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25    gacatccaga tgaccagag cccagcagc ctgagcgcca gcgtgggcga ccgcgtgacc 60
    atcacctgcc gcgccagcca gagcatcggc ctgtacctgg cctggtacca gcagaagccc 120
    ggcaaggccc ccaagctgct gatctacgcc gccagcagcc tgcagagcgg cgtgcccagc 180

30    cgcttcagcg gcagcggcag cggcaccgac ttcacctga ccatcagcag cctgcagccc 240
    gaggacttcg ccacctacta ctgccagcag ggcaacaccc tgagctacac cttcggccag 300
    ggcaccaagg tggagatcaa gcgtacggtg gctgcacccat ctgtcttcat cttcccgcc 360
    tctgatgagc agttgaaatc tggaactgcc tctgttgtgt gcctgctgaa taacttctat 420
    cccagagagg ccaaagtaca gtggaaggtg gataacgccc tccaatcggg taactcccag 480
35    gagagtgtca cagagcagga cagcaaggac agcacctaca gcctcagcag caccctgacg 540
    ctgagcaaag cagactacga gaaacacaaa gtctacgcct gcgaagtcac ccatcagggc 600
    ctgagctcgc ccgtcacaaa gagcttcaac aggggagagt gt 642

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<210> 109
 <211> 11
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Candidates 15, 15-1, 15-2, 15-3, 15-4, 15-5, 15-6, 15-9 LCDR1
 composite sequence

<400> 109

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50          Arg Ala Ser Gln Ser Ile Gly Leu Tyr Leu Ala
              1              5              10

```

<210> 110
 <211> 7
 <212> PRT
 <213> Artificial Sequence

<220>

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<223> Candidates 15, 15-1 \026 15-9 LCDR2

<400> 110

5 Ala Ala Ser Ser Leu Gln Ser
1 5

 $\langle 210 \rangle$ 111

$\langle 211 \rangle$ 10

10 <212> PRT

<212> PRT

<213> Artificial Sequence

 $\langle 220 \rangle$

<223> Candidates 15, 15-1, 15-4, 15-7, 15-8 HCDR1 composite sequence

15

<400> 111

Gly Tyr Ser Phe Thr Asn Tyr Trp Val Gly
1 5 10

20

<210> 112

<211> 17

<212> PRT

<213> Artificial Sequence

25

 $\langle 220 \rangle$

<223> Candidates 15, 15-2, 15-3, 15-6, 15-7, 15-8 HCDR2 composite sequence

<400> 112

30

Phe Ile Asp Pro Ser Asp Ser Tyr Thr Asn Tyr Ala Pro Ser Phe Gln
1 5 10 15
Gly

35

<210> 113

<211> 9

<212> PRT

<213> Artificial Sequence

40

<220>

<223> Candidates 15, 15-1 \026 15-9 LCDR3 conmposite sequence

<400> 113

45

Gln Gln Gly Asn Thr Leu Ser Tyr Thr
1 5

<210> 114

50

<211> 17

<212> PRT

<213> Artificial Sequence

 $\langle 220 \rangle$

55

<223> Candidates 15-1 HCDR2

<400> 114

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Arg Ile Asp Pro Ser Asp Ser Tyr Thr Asn Tyr Ala Pro Ser Phe Gln
 1 5 10 15
 Gly

5

<210> 115
 <211> 10
 <212> PRT
 <213> Artificial Sequence

10

<220>
 <223> Candidates 15-2 HCDR1

15

<400> 115

Gly Tyr Ser Phe Thr Asn Tyr Trp Ile Gly
 1 5 10

20

<210> 116
 <211> 10
 <212> PRT
 <213> Artificial Sequence

25

<220>
 <223> Candidates 15-3, 15-5, 15-6, 15-9 HCDR1
 <400> 116

30

Gly Tyr Ser Phe Thr Asn Tyr Trp Ile Ser
 1 5 10

35

<210> 117
 <211> 17
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Candidates 15-4 HCDR2

40

<400> 117

Phe Ile Asp Pro Ser Asp Ser Tyr Thr Asn Tyr Ser Pro Ser Phe Gln
 1 5 10 15
 Gly

45

<210> 118
 <211> 17
 <212> PRT
 <213> Artificial Sequence

50

<220>
 <223> Candidates 15-5, 15-9 HCDR2

55

<400> 118

EP 2 350 304 B1

Arg Ile Asp Pro Ser Asp Ser Tyr Thr Asn Tyr Ser Pro Ser Phe Gln
 1 5 10 15
 Gly

5

<210> 119
 <211> 14
 <212> PRT
 <213> Artificial Sequence

10

<220>
 <223> Candidates 15-6, 15-9 HCDR3

15

<400> 119

Ala Arg Gln Leu Tyr Gln Gly Tyr Met Asp Thr Phe Asp Ser
 1 5 10

20

<210> 120
 <211> 11
 <212> PRT
 <213> Artificial Sequence

25

<220>
 <223> Candidates 15-7 LCDR1

<400> 120

30

Arg Ala Ser Gln Ser Ile Ser Ser Tyr Leu Ala
 1 5 10

35

<210> 121
 <211> 11
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Candidates 15-8 LCDR1

40

<400> 121

Arg Ala Ser Gln Ser Ile Gly Leu Tyr Leu Asn
 1 5 10

45

<210> 122
 <211> 107
 <212> PRT
 <213> Artificial Sequence

50

<220>
 <223> Candidates 15-7 VL

<400> 122

55

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	Asp	Ile	Gln	Met	Thr	Gln	Ser	Pro	Ser	Ser	Leu	Ser	Ala	Ser	Val	Gly
	1				5					10					15	
	Asp	Arg	Val	Thr	Ile	Thr	Cys	Arg	Ala	Ser	Gln	Ser	Ile	Ser	Ser	Tyr
				20					25					30		
5	Leu	Ala	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Lys	Ala	Pro	Lys	Leu	Leu	Ile
			35				40						45			
	Tyr	Ala	Ala	Ser	Ser	Leu	Gln	Ser	Gly	Val	Pro	Ser	Arg	Phe	Ser	Gly
		50					55					60				
	Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Thr	Ile	Ser	Ser	Leu	Gln	Pro
10	65					70					75					80
	Glu	Asp	Phe	Ala	Thr	Tyr	Tyr	Cys	Gln	Gln	Gly	Asn	Thr	Leu	Ser	Tyr
					85					90					95	
	Thr	Phe	Gly	Gln	Gly	Thr	Lys	Val	Glu	Ile	Lys					
				100					105							

<210> 123
 <211> 107
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Candidates 15-8 VL

<400> 123

	Asp	Ile	Gln	Met	Thr	Gln	Ser	Pro	Ser	Ser	Leu	Ser	Ala	Ser	Val	Gly
	1				5					10					15	
	Asp	Arg	Val	Thr	Ile	Thr	Cys	Arg	Ala	Ser	Gln	Ser	Ile	Gly	Leu	Tyr
				20					25					30		
30	Leu	Asn	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Lys	Ala	Pro	Lys	Leu	Leu	Ile
			35				40						45			
	Tyr	Ala	Ala	Ser	Ser	Leu	Gln	Ser	Gly	Val	Pro	Ser	Arg	Phe	Ser	Gly
		50					55					60				
	Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Thr	Ile	Ser	Ser	Leu	Gln	Pro
35	65					70					75					80
	Glu	Asp	Phe	Ala	Thr	Tyr	Tyr	Cys	Gln	Gln	Gly	Asn	Thr	Leu	Ser	Tyr
					85					90					95	
	Thr	Phe	Gly	Gln	Gly	Thr	Lys	Val	Glu	Ile	Lys					
				100					105							

<210> 124
 <211> 121
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Candidates 15-1 VH

<400> 124

	Glu	Val	Gln	Leu	Val	Gln	Ser	Gly	Ala	Glu	Val	Lys	Lys	Pro	Gly	Glu
	1				5					10					15	
	Ser	Leu	Lys	Ile	Ser	Cys	Lys	Gly	Ser	Gly	Tyr	Ser	Phe	Thr	Asn	Tyr

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			20					25					30			
	Trp	Val	Gly	Trp	Val	Arg	Gln	Met	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Met
			35					40					45			
5	Gly	Arg	Ile	Asp	Pro	Ser	Asp	Ser	Tyr	Thr	Asn	Tyr	Ala	Pro	Ser	Phe
		50					55					60				
	Gln	Gly	Gln	Val	Thr	Ile	Ser	Ala	Asp	Lys	Ser	Ile	Ser	Thr	Ala	Tyr
	65					70					75				80	
	Leu	Gln	Trp	Ser	Ser	Leu	Lys	Ala	Ser	Asp	Thr	Ala	Met	Tyr	Tyr	Cys
				85						90				95		
10	Ala	Arg	Glu	Leu	Tyr	Gln	Gly	Tyr	Met	Asp	Thr	Phe	Asp	Ser	Trp	Gly
				100					105					110		
	Gln	Gly	Thr	Leu	Val	Thr	Val	Ser	Ser							
			115					120								

15 <210> 125
 <211> 121
 <212> PRT
 <213> Artificial Sequence

20 <220>
 <223> Candidate 15-2 VH

<400> 125

25	Glu	Val	Gln	Leu	Val	Gln	Ser	Gly	Ala	Glu	Val	Lys	Lys	Pro	Gly	Glu
	1			5						10					15	
	Ser	Leu	Lys	Ile	Ser	Cys	Lys	Gly	Ser	Gly	Tyr	Ser	Phe	Thr	Asn	Tyr
				20				25					30			
	Trp	Ile	Gly	Trp	Val	Arg	Gln	Met	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Met
30			35					40					45			
	Gly	Phe	Ile	Asp	Pro	Ser	Asp	Ser	Tyr	Thr	Asn	Tyr	Ala	Pro	Ser	Phe
		50					55					60				
	Gln	Gly	Gln	Val	Thr	Ile	Ser	Ala	Asp	Lys	Ser	Ile	Ser	Thr	Ala	Tyr
	65					70					75				80	
	Leu	Gln	Trp	Ser	Ser	Leu	Lys	Ala	Ser	Asp	Thr	Ala	Met	Tyr	Tyr	Cys
35				85						90				95		
	Ala	Arg	Glu	Leu	Tyr	Gln	Gly	Tyr	Met	Asp	Thr	Phe	Asp	Ser	Trp	Gly
				100					105					110		
	Gln	Gly	Thr	Leu	Val	Thr	Val	Ser	Ser							
			115					120								

40 <210> 126
 <211> 121
 <212> PRT
 <213> Artificial Sequence

45 <220>
 <223> Candidate 15-3 VH

<400> 126

50

55

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5 Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
 1 5 10 15
 Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Asn Tyr
 20 25 30
 Trp Ile Ser Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
 35 40 45
 Gly Phe Ile Asp Pro Ser Asp Ser Tyr Thr Asn Tyr Ala Pro Ser Phe
 50 55 60
10 Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
 65 70 75 80
 Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
 85 90 95

15 Ala Arg Glu Leu Tyr Gln Gly Tyr Met Asp Thr Phe Asp Ser Trp Gly
 100 105 110
 Gln Gly Thr Leu Val Thr Val Ser Ser
 115 120

20 <210> 127
 <211> 121
 <212> PRT
 <213> Artificial Sequence

25 <220>
 <223> Candidate 15-4 VH

<400> 127

30 Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
 1 5 10 15
 Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Asn Tyr
 20 25 30
 Trp Val Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
 35 40 45
35 Gly Phe Ile Asp Pro Ser Asp Ser Tyr Thr Asn Tyr Ser Pro Ser Phe
 50 55 60
 Gln Gly His Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
 65 70 75 80
 Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
 85 90 95
40 Ala Arg Glu Leu Tyr Gln Gly Tyr Met Asp Thr Phe Asp Ser Trp Gly
 100 105 110
 Gln Gly Thr Leu Val Thr Val Ser Ser
 115 120

45 <210> 128
 <211> 121
 <212> PRT
 <213> Artificial Sequence

50 <220>
 <223> Candidate 15-5 VH

<400> 128

55

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	Glu	Val	Gln	Leu	Val	Gln	Ser	Gly	Ala	Glu	Val	Lys	Lys	Pro	Gly	Glu
	1				5					10					15	
	Ser	Leu	Lys	Ile	Ser	Cys	Lys	Gly	Ser	Gly	Tyr	Ser	Phe	Thr	Asn	Tyr
				20					25					30		
5	Trp	Ile	Ser	Trp	Val	Arg	Gln	Met	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Met
			35					40					45			
	Gly	Arg	Ile	Asp	Pro	Ser	Asp	Ser	Tyr	Thr	Asn	Tyr	Ser	Pro	Ser	Phe
		50					55					60				
	Gln	Gly	His	Val	Thr	Ile	Ser	Ala	Asp	Lys	Ser	Ile	Ser	Thr	Ala	Tyr
10		65				70					75					80
	Leu	Gln	Trp	Ser	Ser	Leu	Lys	Ala	Ser	Asp	Thr	Ala	Met	Tyr	Tyr	Cys
					85					90					95	
	Ala	Arg	Glu	Leu	Tyr	Gln	Gly	Tyr	Met	Asp	Thr	Phe	Asp	Ser	Trp	Gly
				100					105					110		
15	Gln	Gly	Thr	Leu	Val	Thr	Val	Ser	Ser							
			115					120								

<210> 129

<211> 121

<212> PRT

20 <213> Artificial Sequence

<220>

<223> Candidate 15-6 VH

25 <400> 129

	Glu	Val	Gln	Leu	Val	Gln	Ser	Gly	Ala	Glu	Val	Lys	Lys	Pro	Gly	Glu
	1				5					10					15	
	Ser	Leu	Lys	Ile	Ser	Cys	Lys	Gly	Ser	Gly	Tyr	Ser	Phe	Thr	Asn	Tyr
				20					25					30		
30	Trp	Ile	Ser	Trp	Val	Arg	Gln	Met	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Met
			35					40					45			
	Gly	Phe	Ile	Asp	Pro	Ser	Asp	Ser	Tyr	Thr	Asn	Tyr	Ala	Pro	Ser	Phe
		50					55					60				
35	Gln	Gly	Gln	Val	Thr	Ile	Ser	Ala	Asp	Lys	Ser	Ile	Ser	Thr	Ala	Tyr
		65				70					75					80
	Leu	Gln	Trp	Ser	Ser	Leu	Lys	Ala	Ser	Asp	Thr	Ala	Met	Tyr	Tyr	Cys
					85					90					95	
	Ala	Arg	Gln	Leu	Tyr	Gln	Gly	Tyr	Met	Asp	Thr	Phe	Asp	Ser	Trp	Gly
				100					105					110		
40	Gln	Gly	Thr	Leu	Val	Thr	Val	Ser	Ser							
			115					120								

<210> 130

<211> 448

45 <212> PRT

<213> Artificial Sequence

<220>

<223> Candidate 15-1 full length heavy chain

50 <400> 130

55

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	Glu	Val	Gln	Leu	Val	Gln	Ser	Gly	Ala	Glu	Val	Lys	Lys	Pro	Gly	Glu
	1				5					10					15	
	Ser	Leu	Lys	Ile	Ser	Cys	Lys	Gly	Ser	Gly	Tyr	Ser	Phe	Thr	Asn	Tyr
				20					25					30		
5	Trp	Val	Gly	Trp	Val	Arg	Gln	Met	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Met
			35					40					45			
	Gly	Arg	Ile	Asp	Pro	Ser	Asp	Ser	Tyr	Thr	Asn	Tyr	Ala	Pro	Ser	Phe
		50					55					60				
10	Gln	Gly	Gln	Val	Thr	Ile	Ser	Ala	Asp	Lys	Ser	Ile	Ser	Thr	Ala	Tyr
		65				70					75					80
	Leu	Gln	Trp	Ser	Ser	Leu	Lys	Ala	Ser	Asp	Thr	Ala	Met	Tyr	Tyr	Cys
					85					90					95	
	Ala	Arg	Glu	Leu	Tyr	Gln	Gly	Tyr	Met	Asp	Thr	Phe	Asp	Ser	Trp	Gly
				100					105					110		
15	Gln	Gly	Thr	Leu	Val	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro	Ser
			115						120				125			
	Val	Phe	Pro	Leu	Ala	Pro	Cys	Ser	Arg	Ser	Thr	Ser	Glu	Ser	Thr	Ala
		130					135					140				
	Ala	Leu	Gly	Cys	Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val
		145				150					155					160
20	Ser	Trp	Asn	Ser	Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro	Ala
					165					170					175	
	Val	Leu	Gln	Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val
				180					185					190		
25	Pro	Ser	Ser	Ser	Leu	Gly	Thr	Lys	Thr	Tyr	Thr	Cys	Asn	Val	Asp	His
			195					200					205			
	Lys	Pro	Ser	Asn	Thr	Lys	Val	Asp	Lys	Arg	Val	Glu	Ser	Lys	Tyr	Gly
		210					215					220				
	Pro	Pro	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Ala	Ala	Gly	Gly	Pro	Ser
		225				230					235					240
30																
	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser	Arg
					245					250					255	
	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	Gln	Glu	Asp	Pro
				260						265				270		
35	Glu	Val	Gln	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn	Ala
			275					280					285			
	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Phe	Asn	Ser	Thr	Tyr	Arg	Val	Val
		290					295					300				
40	Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu	Tyr
						310					315					320
	Lys	Cys	Lys	Val	Ser	Asn	Lys	Gly	Leu	Pro	Ser	Ser	Ile	Glu	Lys	Thr
					325					330					335	
	Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr	Leu
				340					345					350		
45	Pro	Pro	Ser	Gln	Glu	Glu	Met	Thr	Lys	Asn	Gln	Val	Ser	Leu	Thr	Cys
				355				360					365			
	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu	Ser
		370					375					380				
	Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Val	Leu	Asp
		385				390					395					400
50	Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser	Arg	Leu	Thr	Val	Asp	Lys	Ser
					405					410					415	
	Arg	Trp	Gln	Glu	Gly	Asn	Val	Phe	Ser	Cys	Ser	Val	Met	His	Glu	Ala
				420					425					430		
55	Leu	His	Asn	His	Tyr	Thr	Gln	Lys	Ser	Leu	Ser	Leu	Ser	Leu	Gly	Lys
			435					440					445			

<210> 131

<211> 448

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<212> PRT

<213> Artificial Sequence

<220>

5 <223> Candidate 15-2 full length heavy chain

<400> 131

10	Glu	Val	Gln	Leu	Val	Gln	Ser	Gly	Ala	Glu	Val	Lys	Lys	Pro	Gly	Glu
	1				5					10					15	
	Ser	Leu	Lys	Ile	Ser	Cys	Lys	Gly	Ser	Gly	Tyr	Ser	Phe	Thr	Asn	Tyr
				20					25					30		
	Trp	Ile	Gly	Trp	Val	Arg	Gln	Met	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Met
			35					40					45			
15	Gly	Phe	Ile	Asp	Pro	Ser	Asp	Ser	Tyr	Thr	Asn	Tyr	Ala	Pro	Ser	Phe
	50						55					60				
	Gln	Gly	Gln	Val	Thr	Ile	Ser	Ala	Asp	Lys	Ser	Ile	Ser	Thr	Ala	Tyr
	65					70					75					80
	Leu	Gln	Trp	Ser	Ser	Leu	Lys	Ala	Ser	Asp	Thr	Ala	Met	Tyr	Tyr	Cys
					85					90					95	
20	Ala	Arg	Glu	Leu	Tyr	Gln	Gly	Tyr	Met	Asp	Thr	Phe	Asp	Ser	Trp	Gly
				100					105					110		
	Gln	Gly	Thr	Leu	Val	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro	Ser
			115					120					125			
25	Val	Phe	Pro	Leu	Ala	Pro	Cys	Ser	Arg	Ser	Thr	Ser	Glu	Ser	Thr	Ala
	130						135					140				
	Ala	Leu	Gly	Cys	Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val
	145					150					155					160
	Ser	Trp	Asn	Ser	Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro	Ala
					165					170					175	
30	Val	Leu	Gln	Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val
				180					185					190		
	Pro	Ser	Ser	Ser	Leu	Gly	Thr	Lys	Thr	Tyr	Thr	Cys	Asn	Val	Asp	His
			195					200					205			

35

40

45

50

55

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	Lys	Pro	Ser	Asn	Thr	Lys	Val	Asp	Lys	Arg	Val	Glu	Ser	Lys	Tyr	Gly
	210						215					220				
	Pro	Pro	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Ala	Ala	Gly	Gly	Pro	Ser
5	225					230					235					240
	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser	Arg
					245					250					255	
	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	Gln	Glu	Asp	Pro
				260						265				270		
10	Glu	Val	Gln	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn	Ala
			275					280					285			
	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Phe	Asn	Ser	Thr	Tyr	Arg	Val	Val
	290					295						300				
	Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu	Tyr
	305				310						315					320
15	Lys	Cys	Lys	Val	Ser	Asn	Lys	Gly	Leu	Pro	Ser	Ser	Ile	Glu	Lys	Thr
				325						330				335		
	Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr	Leu
				340					345					350		
	Pro	Pro	Ser	Gln	Glu	Glu	Met	Thr	Lys	Asn	Gln	Val	Ser	Leu	Thr	Cys
			355					360					365			
20	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu	Ser
	370						375					380				
	Asn	Gly	Gln	Pro	Glu	Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Val	Leu	Asp	
	385				390					395					400	
25	Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser	Arg	Leu	Thr	Val	Asp	Lys	Ser
				405						410				415		
	Arg	Trp	Gln	Glu	Gly	Asn	Val	Phe	Ser	Cys	Ser	Val	Met	His	Glu	Ala
			420					425					430			
	Leu	His	Asn	His	Tyr	Thr	Gln	Lys	Ser	Leu	Ser	Leu	Ser	Leu	Gly	Lys
			435				440					445				

<210> 132

<211> 448

<212> PRT

<213> Artificial Sequence

<220>

<223> Candidate 15-3 full length heavy chain

<400> 132

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	Glu	Val	Gln	Leu	Val	Gln	Ser	Gly	Ala	Glu	Val	Lys	Lys	Pro	Gly	Glu
	1				5					10					15	
	Ser	Leu	Lys	Ile	Ser	Cys	Lys	Gly	Ser	Gly	Tyr	Ser	Phe	Thr	Asn	Tyr
				20					25					30		
5	Trp	Ile	Ser	Trp	Val	Arg	Gln	Met	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Met
			35					40					45			
	Gly	Phe	Ile	Asp	Pro	Ser	Asp	Ser	Tyr	Thr	Asn	Tyr	Ala	Pro	Ser	Phe
		50					55					60				
10	Gln	Gly	Gln	Val	Thr	Ile	Ser	Ala	Asp	Lys	Ser	Ile	Ser	Thr	Ala	Tyr
	65					70					75					80
	Leu	Gln	Trp	Ser	Ser	Leu	Lys	Ala	Ser	Asp	Thr	Ala	Met	Tyr	Tyr	Cys
					85					90					95	
	Ala	Arg	Glu	Leu	Tyr	Gln	Gly	Tyr	Met	Asp	Thr	Phe	Asp	Ser	Trp	Gly
				100					105					110		
15	Gln	Gly	Thr	Leu	Val	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro	Ser
			115					120					125			
	Val	Phe	Pro	Leu	Ala	Pro	Cys	Ser	Arg	Ser	Thr	Ser	Glu	Ser	Thr	Ala
		130					135					140				
	Ala	Leu	Gly	Cys	Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val
	145					150					155					160
20	Ser	Trp	Asn	Ser	Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro	Ala
					165					170					175	
	Val	Leu	Gln	Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val
				180					185					190		
25	Pro	Ser	Ser	Ser	Leu	Gly	Thr	Lys	Thr	Tyr	Thr	Cys	Asn	Val	Asp	His
			195					200					205			
	Lys	Pro	Ser	Asn	Thr	Lys	Val	Asp	Lys	Arg	Val	Glu	Ser	Lys	Tyr	Gly
		210					215					220				
30	Pro	Pro	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Ala	Ala	Gly	Gly	Pro	Ser
	225					230					235					240
	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser	Arg
					245					250					255	
	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	Gln	Glu	Asp	Pro
				260					265					270		
35	Glu	Val	Gln	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn	Ala
			275					280					285			
	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Phe	Asn	Ser	Thr	Tyr	Arg	Val	Val
		290					295					300				
	Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu	Tyr
	305					310					315					320
40	Lys	Cys	Lys	Val	Ser	Asn	Lys	Gly	Leu	Pro	Ser	Ser	Ile	Glu	Lys	Thr
					325					330					335	
	Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr	Leu
				340					345					350		
45	Pro	Pro	Ser	Gln	Glu	Glu	Met	Thr	Lys	Asn	Gln	Val	Ser	Leu	Thr	Cys
			355					360					365			
	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu	Ser
		370					375					380				
	Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Val	Leu	Asp
	385					390					395					400
50	Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser	Arg	Leu	Thr	Val	Asp	Lys	Ser
					405					410					415	
	Arg	Trp	Gln	Glu	Gly	Asn	Val	Phe	Ser	Cys	Ser	Val	Met	His	Glu	Ala
				420					425					430		
	Leu	His	Asn	His	Tyr	Thr	Gln	Lys	Ser	Leu	Ser	Leu	Ser	Leu	Gly	Lys
			435					440					445			

<210> 133
 <211> 448
 <212> PRT

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<213> Artificial Sequence

<220>

<223> Candidate 15-4 full length heavy chain

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<400> 133

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10	Ser	Leu	Lys	Ile	Ser	Cys	Lys	Gly	Ser	Gly	Tyr	Ser	Phe	Thr	Asn	Tyr
				20					25					30		
	Trp	Val	Gly	Trp	Val	Arg	Gln	Met	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Met
			35					40					45			
	Gly	Phe	Ile	Asp	Pro	Ser	Asp	Ser	Tyr	Thr	Asn	Tyr	Ser	Pro	Ser	Phe
15		50					55					60				
	Gln	Gly	His	Val	Thr	Ile	Ser	Ala	Asp	Lys	Ser	Ile	Ser	Thr	Ala	Tyr
	65					70					75				80	
	Leu	Gln	Trp	Ser	Ser	Leu	Lys	Ala	Ser	Asp	Thr	Ala	Met	Tyr	Tyr	Cys
					85					90				95		
20	Ala	Arg	Glu	Leu	Tyr	Gln	Gly	Tyr	Met	Asp	Thr	Phe	Asp	Ser	Trp	Gly
				100					105					110		
	Gln	Gly	Thr	Leu	Val	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro	Ser
			115					120					125			
	Val	Phe	Pro	Leu	Ala	Pro	Cys	Ser	Arg	Ser	Thr	Ser	Glu	Ser	Thr	Ala
25		130					135					140				

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	Ala	Leu	Gly	Cys	Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val
	145					150					155					160
	Ser	Trp	Asn	Ser	Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro	Ala
					165					170					175	
5	Val	Leu	Gln	Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val
				180					185					190		
	Pro	Ser	Ser	Ser	Leu	Gly	Thr	Lys	Thr	Tyr	Thr	Cys	Asn	Val	Asp	His
			195					200					205			
10	Lys	Pro	Ser	Asn	Thr	Lys	Val	Asp	Lys	Arg	Val	Glu	Ser	Lys	Tyr	Gly
		210					215					220				
	Pro	Pro	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Ala	Ala	Gly	Gly	Pro	Ser
	225					230					235					240
	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser	Arg
					245					250					255	
15	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	Gln	Glu	Asp	Pro
				260						265				270		
	Glu	Val	Gln	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn	Ala
			275					280					285			
	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Phe	Asn	Ser	Thr	Tyr	Arg	Val	Val
		290					295					300				
20	Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu	Tyr
	305					310					315					320
	Lys	Cys	Lys	Val	Ser	Asn	Lys	Gly	Leu	Pro	Ser	Ser	Ile	Glu	Lys	Thr
					325					330				335		
25	Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr	Leu
			340						345					350		
	Pro	Pro	Ser	Gln	Glu	Glu	Met	Thr	Lys	Asn	Gln	Val	Ser	Leu	Thr	Cys
			355					360					365			
	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu	Ser
		370					375				380					
30	Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Val	Leu	Asp
	385					390					395					400
	Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser	Arg	Leu	Thr	Val	Asp	Lys	Ser
					405					410				415		
	Arg	Trp	Gln	Glu	Gly	Asn	Val	Phe	Ser	Cys	Ser	Val	Met	His	Glu	Ala
			420					425					430			
35	Leu	His	Asn	His	Tyr	Thr	Gln	Lys	Ser	Leu	Ser	Leu	Ser	Leu	Gly	Lys
			435					440					445			

<210> 134

<211> 448

40 <212> PRT

<213> Artificial Sequence

<220>

<223> Candidate 15-5 full length heavy chain

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<400> 134

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	Glu	Val	Gln	Leu	Val	Gln	Ser	Gly	Ala	Glu	Val	Lys	Lys	Pro	Gly	Glu
	1				5					10					15	
	Ser	Leu	Lys	Ile	Ser	Cys	Lys	Gly	Ser	Gly	Tyr	Ser	Phe	Thr	Asn	Tyr
				20					25					30		
5	Trp	Ile	Ser	Trp	Val	Arg	Gln	Met	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Met
			35					40					45			
	Gly	Arg	Ile	Asp	Pro	Ser	Asp	Ser	Tyr	Thr	Asn	Tyr	Ser	Pro	Ser	Phe
		50					55					60				
	Gln	Gly	His	Val	Thr	Ile	Ser	Ala	Asp	Lys	Ser	Ile	Ser	Thr	Ala	Tyr
10		65				70					75					80
	Leu	Gln	Trp	Ser	Ser	Leu	Lys	Ala	Ser	Asp	Thr	Ala	Met	Tyr	Tyr	Cys
					85					90					95	
	Ala	Arg	Glu	Leu	Tyr	Gln	Gly	Tyr	Met	Asp	Thr	Phe	Asp	Ser	Trp	Gly
				100					105					110		
15																
	Gln	Gly	Thr	Leu	Val	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro	Ser
			115					120					125			
	Val	Phe	Pro	Leu	Ala	Pro	Cys	Ser	Arg	Ser	Thr	Ser	Glu	Ser	Thr	Ala
		130					135					140				
20	Ala	Leu	Gly	Cys	Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val
		145				150					155					160
	Ser	Trp	Asn	Ser	Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro	Ala
					165					170					175	
	Val	Leu	Gln	Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val
25				180				185						190		
	Pro	Ser	Ser	Ser	Leu	Gly	Thr	Lys	Thr	Tyr	Thr	Cys	Asn	Val	Asp	His
			195					200					205			
	Lys	Pro	Ser	Asn	Thr	Lys	Val	Asp	Lys	Arg	Val	Glu	Ser	Lys	Tyr	Gly
		210					215					220				
30	Pro	Pro	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Ala	Ala	Gly	Gly	Pro	Ser
		225				230					235					240
	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser	Arg
				245						250					255	
	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	Gln	Glu	Asp	Pro
35				260					265					270		
	Glu	Val	Gln	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn	Ala
			275					280					285			
	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Phe	Asn	Ser	Thr	Tyr	Arg	Val	Val
		290					295					300				
40	Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu	Tyr
					310						315					320
	Lys	Cys	Lys	Val	Ser	Asn	Lys	Gly	Leu	Pro	Ser	Ser	Ile	Glu	Lys	Thr
				325						330					335	
	Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr	Leu
			340						345					350		
45	Pro	Pro	Ser	Gln	Glu	Glu	Met	Thr	Lys	Asn	Gln	Val	Ser	Leu	Thr	Cys
			355					360					365			
	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu	Ser
		370					375					380				
	Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Val	Leu	Asp
		385				390					395					400
50	Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser	Arg	Leu	Thr	Val	Asp	Lys	Ser
				405						410					415	
	Arg	Trp	Gln	Glu	Gly	Asn	Val	Phe	Ser	Cys	Ser	Val	Met	His	Glu	Ala
			420						425					430		
55	Leu	His	Asn	His	Tyr	Thr	Gln	Lys	Ser	Leu	Ser	Leu	Ser	Leu	Gly	Lys
			435					440					445			

<210> 135

<211> 448

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<212> PRT

<213> Artificial Sequence

<220>

5 <223> Candidate 15-6 full length heavy chain

<400> 135

10	Glu	Val	Gln	Leu	Val	Gln	Ser	Gly	Ala	Glu	Val	Lys	Lys	Pro	Gly	Glu
	1				5					10					15	
	Ser	Leu	Lys	Ile	Ser	Cys	Lys	Gly	Ser	Gly	Tyr	Ser	Phe	Thr	Asn	Tyr
				20					25					30		
	Trp	Ile	Ser	Trp	Val	Arg	Gln	Met	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Met
			35					40					45			
15	Gly	Phe	Ile	Asp	Pro	Ser	Asp	Ser	Tyr	Thr	Asn	Tyr	Ala	Pro	Ser	Phe
		50					55					60				
	Gln	Gly	Gln	Val	Thr	Ile	Ser	Ala	Asp	Lys	Ser	Ile	Ser	Thr	Ala	Tyr
	65					70					75					80

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	Leu	Gln	Trp	Ser	Ser	Leu	Lys	Ala	Ser	Asp	Thr	Ala	Met	Tyr	Tyr	Cys
					85					90					95	
	Ala	Arg	Gln	Leu	Tyr	Gln	Gly	Tyr	Met	Asp	Thr	Phe	Asp	Ser	Trp	Gly
				100					105					110		
5	Gln	Gly	Thr	Leu	Val	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro	Ser
			115					120					125			
	Val	Phe	Pro	Leu	Ala	Pro	Cys	Ser	Arg	Ser	Thr	Ser	Glu	Ser	Thr	Ala
		130					135					140				
	Ala	Leu	Gly	Cys	Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val
10		145				150					155					160
	Ser	Trp	Asn	Ser	Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro	Ala
				165						170					175	
	Val	Leu	Gln	Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val
				180					185					190		
	Pro	Ser	Ser	Ser	Leu	Gly	Thr	Lys	Thr	Tyr	Thr	Cys	Asn	Val	Asp	His
15			195					200					205			
	Lys	Pro	Ser	Asn	Thr	Lys	Val	Asp	Lys	Arg	Val	Glu	Ser	Lys	Tyr	Gly
		210					215					220				
	Pro	Pro	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Ala	Gly	Gly	Pro	Ser	
		225				230				235					240	
20	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser	Arg
				245						250					255	
	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	Gln	Glu	Asp	Pro
			260						265					270		
	Glu	Val	Gln	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn	Ala
25			275						280				285			
	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Phe	Asn	Ser	Thr	Tyr	Arg	Val	Val
		290				295					300					
	Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu	Tyr
		305				310					315					320
30	Lys	Cys	Lys	Val	Ser	Asn	Lys	Gly	Leu	Pro	Ser	Ser	Ile	Glu	Lys	Thr
				325						330				335		
	Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr	Leu
			340						345					350		
	Pro	Pro	Ser	Gln	Glu	Glu	Met	Thr	Lys	Asn	Gln	Val	Ser	Leu	Thr	Cys
			355					360					365			
35	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu	Ser
		370				375					380					
	Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Val	Leu	Asp
		385				390					395					400
	Ser	Asp	Gly	Ser	Phe	Leu	Tyr	Ser	Arg	Leu	Thr	Val	Asp	Lys	Ser	
				405					410					415		
40	Arg	Trp	Gln	Glu	Gly	Asn	Val	Phe	Ser	Cys	Ser	Val	Met	His	Glu	Ala
			420						425					430		
	Leu	His	Asn	His	Tyr	Thr	Gln	Lys	Ser	Leu	Ser	Leu	Ser	Leu	Gly	Lys
			435					440					445			

45 <210> 136
 <211> 40
 <212> DNA
 <213> Artificial Sequence

50 <220>
 <223> Primer

<400> 136
 ccttaccat aatcaactcg agagattacc agccgccaac 40

55 <210> 137
 <211> 49
 <212> DNA

<213> Artificial Sequence

<220>

<223> Primer

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<400> 137

caagagcttc tattatcaaa caatgagatt caagcgctaa aaagtgaag 49

<210> 138

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<211> 45

<212> DNA

<213> Artificial Sequence

<220>

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<223> Primer

<400> 138

ccttacacat actcaaccta accgagaata aaatctcaaa aatag 45

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<210> 139

<211> 47

<212> DNA

<213> Artificial Sequence

<220>

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<223> Primer

<400> 139

gaaatctatc ttctctacaa cgaggccctg cagctgacta ggaactc 47

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<210> 140

<211> 58

<212> DNA

<213> Artificial Sequence

35

<220>

<223> Primer

<400> 140

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gccttcaacg actgatgctc gaggaggtgg cccttgagaa tgtggatagc tctccttc 58

<210> 141

<211> 39

<212> DNA

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<213> Artificial Sequence

<220>

<223> Primer

<400> 141

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gtacctgcag ctgtctacga gctcctttgc cttggtccc 39

<210> 142

<211> 33

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<212> DNA

<213> Artificial Sequence

<220>

<223> Primer

<400> 142

gcctggagtg gatgggccgg atcgaccca gcg 33

5

<210> 143

<211> 33

<212> DNA

<213> Artificial Sequence

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<220>

<223> Primer

<400> 143

cgctggggtc gatccggccc atccactcca ggc 33

15

<210> 144

<211> 20

<212> DNA

<213> Artificial Sequence

20

<220>

<223> Primer

<400> 144

agaggtact cccgttgcg 20

25

<210> 145

<211> 38

<212> DNA

<213> Artificial Sequence

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<220>

<223> Primer

<400> 145

gcatctggcg caccagccg atccagtagt tgggaag 38

35

<210> 146

<211> 20

<212> DNA

<213> Artificial Sequence

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<220>

<223> Primer

<400> 146

agaggtact cccgttgcg 20

45

<210> 147

<211> 38

<212> DNA

<213> Artificial Sequence

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<220>

<223> Primer

<400> 147

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gcatctggcg caccagctg atccagtagt tgggaag 38

5 <210> 148
<211> 47
<212> DNA
<213> Artificial Sequence

10 <220>
<223> Primer

<400> 148
cgctgatggt cacgtggccc tggaagctag ggctgtagtt ggtgtag 47

15 <210> 149
<211> 38
<212> DNA
<213> Artificial Sequence

20 <220>
<223> Primer

<400> 149
cttcaccaac tactggatca gctgggtgcg ccagatgc 38

25 <210> 150
<211> 40
<212> DNA
<213> Artificial Sequence

30 <220>
<223> Primer

<400> 150
cgccatgtac tactgcgccc gccagctgta ccagggctac 40

35 <210> 151
<211> 40
<212> DNA
<213> Artificial Sequence

40 <220>
<223> Primer

45 <400> 151
gtagccctgg tacagctggc gggcgagta gtacatggcg 40

50 <210> 152
<211> 40
<212> DNA
<213> Homo sapiens

<400> 152
gccagccaga gcatcagcag ctacctggcc tggtagcagc 40

55 <210> 153
<211> 40
<212> DNA
<213> Artificial Sequence

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<220>

<223> Primer

<400> 153

5 gctggtacca ggccaggtag ctgctgatgc tctggctggc 40

<210> 154

<211> 43

<212> DNA

10 <213> Artificial Sequence

<220>

<223> Primer

<400> 154

15 cgggcttctg ctggtaccag ttcaggtagc tgctgatgct ctg 43

<210> 155

<211> 214

20 <212> PRT

<213> Artificial Sequence

<220>

<223> Candidate 14 full length light chain

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<400> 155

30	Asp	Ile	Gln	Met	Thr	Gln	Ser	Pro	Ser	Ser	Leu	Ser	Ala	Ser	Val	Gly
	1				5				10					15		
	Asp	Arg	Val	Thr	Ile	Thr	Cys	Arg	Ala	Ser	Gln	Ser	Ile	Gly	Leu	Tyr
			20						25				30			
	Leu	Ala	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Lys	Ala	Pro	Lys	Leu	Leu	Ile
			35					40					45			
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	50						55					60				
	Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Thr	Ile	Ser	Ser	Leu	Gln	Pro
	65					70					75				80	
	Glu	Asp	Phe	Ala	Thr	Tyr	Tyr	Cys	Gln	Gln	Ala	Glu	Thr	Val	Ser	Pro
					85					90					95	
40	Thr	Phe	Gly	Gln	Gly	Thr	Lys	Val	Glu	Ile	Lys	Arg	Thr	Val	Ala	Ala
				100					105					110		
	Pro	Ser	Val	Phe	Ile	Phe	Pro	Pro	Ser	Asp	Glu	Gln	Leu	Lys	Ser	Gly
			115					120					125			
	Thr	Ala	Ser	Val	Val	Cys	Leu	Leu	Asn	Asn	Phe	Tyr	Pro	Arg	Glu	Ala
	130						135					140				
45	Lys	Val	Gln	Trp	Lys	Val	Asp	Asn	Ala	Leu	Gln	Ser	Gly	Asn	Ser	Gln
	145					150					155				160	
	Glu	Ser	Val	Thr	Glu	Gln	Asp	Ser	Lys	Asp	Ser	Thr	Tyr	Ser	Leu	Ser
					165					170					175	
	Ser	Thr	Leu	Thr	Leu	Ser	Lys	Ala	Asp	Tyr	Glu	Lys	His	Lys	Val	Tyr
50				180					185					190		
	Ala	Cys	Glu	Val	Thr	His	Gln	Gly	Leu	Ser	Ser	Pro	Val	Thr	Lys	Ser
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<210> 156

<211> 214

<212> PRT

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<213> Artificial Sequence

<220>

<223> Candidate 15, 15-1, 15-2, 15-3, 15-4, 15-5, 15-6, 15-9 full length
light chain

<400> 156

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      Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Gly Leu Tyr
        20           25           30
      Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35           40           45
15      Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
        50           55           60
      Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
        65           70           75           80
      Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Gly Asn Thr Leu Ser Tyr
        85           90           95

20      Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala
        100           105           110
      Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
        115           120           125
25      Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
        130           135           140
      Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
        145           150           155           160
30      Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
        165           170           175
      Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
        180           185           190
      Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
        195           200           205
35      Phe Asn Arg Gly Glu Cys
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<210> 157

<211> 214

<212> PRT

<213> Artificial Sequence

<220>

<223> Candidate 15-7 full length light chain

<400> 157

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	1				5					10					15	
	Asp	Arg	Val	Thr	Ile	Thr	Cys	Arg	Ala	Ser	Gln	Ser	Ile	Ser	Ser	Tyr
				20					25					30		
5	Leu	Ala	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Lys	Ala	Pro	Lys	Leu	Leu	Ile
			35				40						45			
	Tyr	Ala	Ala	Ser	Ser	Leu	Gln	Ser	Gly	Val	Pro	Ser	Arg	Phe	Ser	Gly
		50					55					60				
	Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Thr	Ile	Ser	Ser	Leu	Gln	Pro
10	65					70					75					80
	Glu	Asp	Phe	Ala	Thr	Tyr	Tyr	Cys	Gln	Gln	Gly	Asn	Thr	Leu	Ser	Tyr
					85					90					95	
	Thr	Phe	Gly	Gln	Gly	Thr	Lys	Val	Glu	Ile	Lys	Arg	Thr	Val	Ala	Ala
				100					105					110		
15	Pro	Ser	Val	Phe	Ile	Phe	Pro	Pro	Ser	Asp	Glu	Gln	Leu	Lys	Ser	Gly
			115				120						125			
	Thr	Ala	Ser	Val	Val	Cys	Leu	Leu	Asn	Asn	Phe	Tyr	Pro	Arg	Glu	Ala
		130					135					140				
	Lys	Val	Gln	Trp	Lys	Val	Asp	Asn	Ala	Leu	Gln	Ser	Gly	Asn	Ser	Gln
	145					150					155					160
20	Glu	Ser	Val	Thr	Glu	Gln	Asp	Ser	Lys	Asp	Ser	Thr	Tyr	Ser	Leu	Ser
					165					170					175	
	Ser	Thr	Leu	Thr	Leu	Ser	Lys	Ala	Asp	Tyr	Glu	Lys	His	Lys	Val	Tyr
				180					185					190		
	Ala	Cys	Glu	Val	Thr	His	Gln	Gly	Leu	Ser	Ser	Pro	Val	Thr	Lys	Ser
25			195					200					205			
	Phe	Asn	Arg	Gly	Glu	Cys										
			210													

30 <210> 158
 <211> 214
 <212> PRT
 <213> Artificial Sequence

 35 <220>
 <223> Candidate 15-8 full length light chain

 <400> 158

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	Asp	Ile	Gln	Met	Thr	Gln	Ser	Pro	Ser	Ser	Leu	Ser	Ala	Ser	Val	Gly
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	Asp	Arg	Val	Thr	Ile	Thr	Cys	Arg	Ala	Ser	Gln	Ser	Ile	Gly	Leu	Tyr
			20					25						30		
5	Leu	Asn	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Lys	Ala	Pro	Lys	Leu	Leu	Ile
		35					40						45			
	Tyr	Ala	Ala	Ser	Ser	Leu	Gln	Ser	Gly	Val	Pro	Ser	Arg	Phe	Ser	Gly
		50					55					60				
	Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Thr	Ile	Ser	Ser	Leu	Gln	Pro
10		65				70					75					80
	Glu	Asp	Phe	Ala	Thr	Tyr	Tyr	Cys	Gln	Gln	Gly	Asn	Thr	Leu	Ser	Tyr
					85					90					95	
	Thr	Phe	Gly	Gln	Gly	Thr	Lys	Val	Glu	Ile	Lys	Arg	Thr	Val	Ala	Ala
				100					105					110		
15	Pro	Ser	Val	Phe	Ile	Phe	Pro	Pro	Ser	Asp	Glu	Gln	Leu	Lys	Ser	Gly
			115				120						125			
	Thr	Ala	Ser	Val	Val	Cys	Leu	Leu	Asn	Asn	Phe	Tyr	Pro	Arg	Glu	Ala
		130					135					140				
	Lys	Val	Gln	Trp	Lys	Val	Asp	Asn	Ala	Leu	Gln	Ser	Gly	Asn	Ser	Gln
		145				150					155					160
20	Glu	Ser	Val	Thr	Glu	Gln	Asp	Ser	Lys	Asp	Ser	Thr	Tyr	Ser	Leu	Ser
					165					170					175	
	Ser	Thr	Leu	Thr	Leu	Ser	Lys	Ala	Asp	Tyr	Glu	Lys	His	Lys	Val	Tyr
				180					185					190		
	Ala	Cys	Glu	Val	Thr	His	Gln	Gly	Leu	Ser	Ser	Pro	Val	Thr	Lys	Ser
25			195					200					205			
	Phe	Asn	Arg	Gly	Glu	Cys										
		210														

30 <210> 159
 <211> 121
 <212> PRT
 <213> Artificial Sequence

35 <220>
 <223> Candidate 15-9 VH

<400> 159

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	Ser	Leu	Lys	Ile	Ser	Cys	Lys	Gly	Ser	Gly	Tyr	Ser	Phe	Thr	Asn	Tyr
				20				25						30		
	Trp	Ile	Ser	Trp	Val	Arg	Gln	Met	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Met
			35				40						45			
45	Gly	Arg	Ile	Asp	Pro	Ser	Asp	Ser	Tyr	Thr	Asn	Tyr	Ser	Pro	Ser	Phe
		50					55					60				
	Gln	Gly	His	Val	Thr	Ile	Ser	Ala	Asp	Lys	Ser	Ile	Ser	Thr	Ala	Tyr
		65				70					75					80
	Leu	Gln	Trp	Ser	Ser	Leu	Lys	Ala	Ser	Asp	Thr	Ala	Met	Tyr	Tyr	Cys
					85					90				95		
50	Ala	Arg	Gln	Leu	Tyr	Gln	Gly	Tyr	Met	Asp	Thr	Phe	Asp	Ser	Trp	Gly
				100					105					110		
	Gln	Gly	Thr	Leu	Val	Thr	Val	Ser	Ser							
				115				120								

55 <210> 160
 <211> 448
 <212> PRT
 <213> Artificial Sequence

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<220>

<223> Candidate 15-9 full length heavy chain

<400> 160

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Ser	Leu	Lys	Ile	Ser	Cys	Lys	Gly	Ser	Gly	Tyr	Ser	Phe	Thr	Asn	Tyr
			20					25					30		
Trp	Ile	Ser	Trp	Val	Arg	Gln	Met	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Met
		35					40					45			
Gly	Arg	Ile	Asp	Pro	Ser	Asp	Ser	Tyr	Thr	Asn	Tyr	Ser	Pro	Ser	Phe
	50					55					60				
Gln	Gly	His	Val	Thr	Ile	Ser	Ala	Asp	Lys	Ser	Ile	Ser	Thr	Ala	Tyr
65					70					75					80
Leu	Gln	Trp	Ser	Ser	Leu	Lys	Ala	Ser	Asp	Thr	Ala	Met	Tyr	Tyr	Cys
				85					90				95		
Ala	Arg	Gln	Leu	Tyr	Gln	Gly	Tyr	Met	Asp	Thr	Phe	Asp	Ser	Trp	Gly
		100						105					110		
Gln	Gly	Thr	Leu	Val	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro	Ser
		115						120				125			
Val	Phe	Pro	Leu	Ala	Pro	Cys	Ser	Arg	Ser	Thr	Ser	Glu	Ser	Thr	Ala
	130					135					140				
Ala	Leu	Gly	Cys	Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val
145					150					155					160
Ser	Trp	Asn	Ser	Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro	Ala
				165					170				175		
Val	Leu	Gln	Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val
			180					185					190		
Pro	Ser	Ser	Ser	Leu	Gly	Thr	Lys	Thr	Tyr	Thr	Cys	Asn	Val	Asp	His
		195					200					205			
Lys	Pro	Ser	Asn	Thr	Lys	Val	Asp	Lys	Arg	Val	Glu	Ser	Lys	Tyr	Gly
	210					215					220				
Pro	Pro	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Ala	Ala	Gly	Gly	Pro	Ser
225					230					235					240
Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser	Arg
				245					250				255		
Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	Gln	Glu	Asp	Pro
			260					265					270		
Glu	Val	Gln	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn	Ala
		275					280					285			
Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Phe	Asn	Ser	Thr	Tyr	Arg	Val	Val
	290					295					300				
Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu	Tyr
305					310					315					320
Lys	Cys	Lys	Val	Ser	Asn	Lys	Gly	Leu	Pro	Ser	Ser	Ile	Glu	Lys	Thr
				325					330				335		
Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr	Leu
			340					345					350		
Pro	Pro	Ser	Gln	Glu	Glu	Met	Thr	Lys	Asn	Gln	Val	Ser	Leu	Thr	Cys
		355					360					365			
Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu	Ser
	370					375				380					
Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Val	Leu	Asp
385					390					395					400
Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser	Arg	Leu	Thr	Val	Asp	Lys	Ser
				405					410				415		
Arg	Trp	Gln	Glu	Gly	Asn	Val	Phe	Ser	Cys	Ser	Val	Met	His	Glu	Ala
			420					425					430		
Leu	His	Asn	His	Tyr	Thr	Gln	Lys	Ser	Leu	Ser	Leu	Ser	Leu	Gly	Lys
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<210> 161
 <211> 2718
 <212> DNA
 <213> Mus musculus

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<400> 161

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<210> 162
 <211> 905
 <212> PRT
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<400> 162

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Ser	Leu	Trp	Ile	Leu	Leu	Val	Ser	Ser	Thr	Asn	Gln	Cys	Thr	Val	Arg

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				20				25				30				
	Tyr	Asn	Val	Ala	Asp	Cys	Ser	His	Leu	Lys	Leu	Thr	His	Ile	Pro	Asp
			35					40					45			
5	Asp	Leu	Pro	Ser	Asn	Ile	Thr	Val	Leu	Asn	Leu	Thr	His	Asn	Gln	Leu
		50					55					60				
	Arg	Arg	Leu	Pro	Pro	Thr	Asn	Phe	Thr	Arg	Tyr	Ser	Gln	Leu	Ala	Ile
	65					70					75					80
	Leu	Asp	Ala	Gly	Phe	Asn	Ser	Ile	Ser	Lys	Leu	Glu	Pro	Glu	Leu	Cys
					85					90					95	
10	Gln	Ile	Leu	Pro	Leu	Leu	Lys	Val	Leu	Asn	Leu	Gln	His	Asn	Glu	Leu
			100						105					110		
	Ser	Gln	Ile	Ser	Asp	Gln	Thr	Phe	Val	Phe	Cys	Thr	Asn	Leu	Thr	Glu
			115					120					125			
	Leu	Asp	Leu	Met	Ser	Asn	Ser	Ile	His	Lys	Ile	Lys	Ser	Asn	Pro	Phe
		130					135					140				
15	Lys	Asn	Gln	Lys	Asn	Leu	Ile	Lys	Leu	Asp	Leu	Ser	His	Asn	Gly	Leu
	145					150					155					160
	Ser	Ser	Thr	Lys	Leu	Gly	Thr	Gly	Val	Gln	Leu	Glu	Asn	Leu	Gln	Glu
					165					170					175	
	Leu	Leu	Leu	Ala	Lys	Asn	Lys	Ile	Leu	Ala	Leu	Arg	Ser	Glu	Glu	Leu
				180					185					190		
20	Glu	Phe	Leu	Gly	Asn	Ser	Ser	Leu	Arg	Lys	Leu	Asp	Leu	Ser	Ser	Asn
			195					200					205			
	Pro	Leu	Lys	Glu	Phe	Ser	Pro	Gly	Cys	Phe	Gln	Thr	Ile	Gly	Lys	Leu
		210					215					220				
	Phe	Ala	Leu	Leu	Leu	Asn	Asn	Ala	Gln	Leu	Asn	Pro	His	Leu	Thr	Glu
	225					230					235					240
25	Lys	Leu	Cys	Trp	Glu	Leu	Ser	Asn	Thr	Ser	Ile	Gln	Asn	Leu	Ser	Leu
					245					250					255	
	Ala	Asn	Asn	Gln	Leu	Leu	Ala	Thr	Ser	Glu	Ser	Thr	Phe	Ser	Gly	Leu
				260				265						270		
	Lys	Trp	Thr	Asn	Leu	Thr	Gln	Leu	Asp	Leu	Ser	Tyr	Asn	Asn	Leu	His
			275				280						285			
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		290					295					300				
	Ser	Leu	Glu	Tyr	Asn	Asn	Ile	Gln	Arg	Leu	Ser	Pro	Arg	Ser	Phe	Tyr
		305				310					315					320
	Gly	Leu	Ser	Asn	Leu	Arg	Tyr	Leu	Ser	Leu	Lys	Arg	Ala	Phe	Thr	Lys
					325					330					335	
35	Gln	Ser	Val	Ser	Leu	Ala	Ser	His	Pro	Asn	Ile	Asp	Asp	Phe	Ser	Phe
					340				345					350		
	Gln	Trp	Leu	Lys	Tyr	Leu	Glu	Tyr	Leu	Asn	Met	Asp	Asp	Asn	Asn	Ile
			355					360					365			
40	Pro	Ser	Thr	Lys	Ser	Asn	Thr	Phe	Thr	Gly	Leu	Val	Ser	Leu	Lys	Tyr
			370				375						380			
	Leu	Ser	Leu	Ser	Lys	Thr	Phe	Thr	Ser	Leu	Gln	Thr	Leu	Thr	Asn	Glu
						390					395					400
	Thr	Phe	Val	Ser	Leu	Ala	His	Ser	Pro	Leu	Leu	Thr	Leu	Asn	Leu	Thr
					405					410					415	
45	Lys	Asn	His	Ile	Ser	Lys	Ile	Ala	Asn	Gly	Thr	Phe	Ser	Trp	Leu	Gly
				420					425					430		
	Gln	Leu	Arg	Ile	Leu	Asp	Leu	Gly	Leu	Asn	Glu	Ile	Glu	Gln	Lys	Leu
			435					440					445			
	Ser	Gly	Gln	Glu	Trp	Arg	Gly	Leu	Arg	Asn	Ile	Phe	Glu	Ile	Tyr	Leu
		450					455					460				
50	Ser	Tyr	Asn	Lys	Tyr	Leu	Gln	Leu	Ser	Thr	Ser	Ser	Phe	Ala	Leu	Val
		465				470					475					480
	Pro	Ser	Leu	Gln	Arg	Leu	Met	Leu	Arg	Arg	Val	Ala	Leu	Lys	Asn	Val
					485					490					495	
	Asp	Ile	Ser	Pro	Ser	Pro	Phe	Arg	Pro	Leu	Arg	Asn	Leu	Thr	Ile	Leu
				500					505					510		
55	Asp	Leu	Ser	Asn	Asn	Asn	Ile	Ala	Asn	Ile	Asn	Glu	Asp	Leu	Leu	Glu
				515				520					525			

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	Gly	Leu	Glu	Asn	Leu	Glu	Ile	Leu	Asp	Phe	Gln	His	Asn	Asn	Leu	Ala
	530						535					540				
	Arg	Leu	Trp	Lys	Arg	Ala	Asn	Pro	Gly	Gly	Pro	Val	Asn	Phe	Leu	Lys
	545					550					555					560
5	Gly	Leu	Ser	His	Leu	His	Ile	Leu	Asn	Leu	Glu	Ser	Asn	Gly	Leu	Asp
					565					570					575	
	Glu	Ile	Pro	Val	Gly	Val	Phe	Lys	Asn	Leu	Phe	Glu	Leu	Lys	Ser	Ile
				580					585					590		
	Asn	Leu	Gly	Leu	Asn	Asn	Leu	Asn	Lys	Leu	Glu	Pro	Phe	Ile	Phe	Asp
10			595					600					605			
	Asp	Gln	Thr	Ser	Leu	Arg	Ser	Leu	Asn	Leu	Gln	Lys	Asn	Leu	Ile	Thr
	610						615					620				
	Ser	Val	Glu	Lys	Asp	Val	Phe	Gly	Pro	Pro	Phe	Gln	Asn	Leu	Asn	Ser
	625					630					635					640
15	Leu	Asp	Met	Arg	Phe	Asn	Pro	Phe	Asp	Cys	Thr	Cys	Glu	Ser	Ile	Ser
					645					650					655	
	Trp	Phe	Val	Asn	Trp	Ile	Asn	Gln	Thr	His	Thr	Asn	Ile	Ser	Glu	Leu
				660					665					670		
	Ser	Thr	His	Tyr	Leu	Cys	Asn	Thr	Pro	His	His	Tyr	Tyr	Gly	Phe	Pro
			675					680				685				
20	Leu	Lys	Leu	Phe	Asp	Thr	Ser	Ser	Cys	Lys	Asp	Ser	Ala	Pro	Phe	Glu
	690						695				700					
	Leu	Leu	Phe	Ile	Ile	Ser	Thr	Ser	Met	Leu	Leu	Val	Phe	Ile	Leu	Val
	705					710				715						720
	Val	Leu	Leu	Ile	His	Ile	Glu	Gly	Trp	Arg	Ile	Ser	Phe	Tyr	Trp	Asn
25					725					730					735	
	Val	Ser	Val	His	Arg	Ile	Leu	Gly	Phe	Lys	Glu	Ile	Asp	Thr	Gln	Ala
				740					745					750		
	Glu	Gln	Phe	Glu	Tyr	Thr	Ala	Tyr	Ile	Ile	His	Ala	His	Lys	Asp	Arg
			755					760					765			
	Asp	Trp	Val	Trp	Glu	His	Phe	Ser	Pro	Met	Glu	Glu	Gln	Asp	Gln	Ser
30		770					775					780				
	Leu	Lys	Phe	Cys	Leu	Glu	Glu	Arg	Asp	Phe	Glu	Ala	Gly	Val	Leu	Gly
	785				790					795						800
	Leu	Glu	Ala	Ile	Val	Asn	Ser	Ile	Lys	Arg	Ser	Arg	Lys	Ile	Ile	Phe
				805						810					815	
35	Val	Ile	Thr	His	His	Leu	Leu	Lys	Asp	Pro	Leu	Cys	Arg	Arg	Phe	Lys
				820					825					830		
	Val	His	His	Ala	Val	Gln	Gln	Ala	Ile	Glu	Gln	Asn	Leu	Asp	Ser	Ile
			835					840					845			
	Ile	Leu	Ile	Phe	Leu	Gln	Asn	Ile	Pro	Asp	Tyr	Lys	Leu	Asn	His	Ala
	850					855					860					
40	Leu	Cys	Leu	Arg	Arg	Gly	Met	Phe	Lys	Ser	His	Cys	Ile	Leu	Asn	Trp
	865				870						875					880
	Pro	Val	Gln	Lys	Glu	Arg	Ile	Asn	Ala	Phe	His	His	Lys	Leu	Gln	Val
					885					890					895	
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<210> 163

<211> 107

<212> PRT

50 <213> Rattus rattus

<400> 163

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	Glu	Thr	Val	Thr	Ile	Glu	Cys	Arg	Ala	Ser	Glu	Asp	Ile	Tyr	Asn	Gly
				20					25					30		
5	Leu	Ala	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Lys	Ser	Pro	Gln	Leu	Leu	Ile
			35					40					45			
	Tyr	Asp	Ser	Asn	Ser	Leu	His	Thr	Gly	Val	Pro	Ser	Arg	Phe	Ser	Gly
10			50				55					60				
	Arg	Gly	Ser	Gly	Thr	Gln	Tyr	Ser	Leu	Arg	Ile	Asn	Ser	Leu	Gln	Ser
	65					70					75					80
	Glu	Asp	Val	Ala	Ser	Tyr	Phe	Cys	Gln	Gln	Tyr	Tyr	Asp	Tyr	Pro	Leu
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	Thr	Phe	Gly	Ser	Gly	Thr	Lys	Leu	Glu	Ile	Lys					
15				100					105							

<210> 164
<211> 119
<212> PRT
<213> Rattus rattus

<400> 164

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40 <210> 165
 <211> 234
 <212> PRT
 <213> Artificial Sequence

45 <220>
 <223> Hybrid of rat variable region and mouse constant region

<400> 165

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	Asp	Ala	Ile	Cys	Asp	Ile	Gln	Met	Thr	Gln	Ser	Pro	Thr	Ser	Leu	Ser
				20					25					30		
5	Ala	Ser	Leu	Gly	Glu	Thr	Val	Thr	Ile	Glu	Cys	Arg	Ala	Ser	Glu	Asp
			35					40					45			
	Ile	Tyr	Asn	Gly	Leu	Ala	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Lys	Ser	Pro
	50						55					60				
	Gln	Leu	Leu	Ile	Tyr	Asp	Ser	Asn	Ser	Leu	His	Thr	Gly	Val	Pro	Ser
10	65				70					75						80
	Arg	Phe	Ser	Gly	Arg	Gly	Ser	Gly	Thr	Gln	Tyr	Ser	Leu	Arg	Ile	Asn
				85						90					95	
	Ser	Leu	Gln	Ser	Glu	Asp	Val	Ala	Ser	Tyr	Phe	Cys	Gln	Gln	Tyr	Tyr
				100					105					110		
15	Asp	Tyr	Pro	Leu	Thr	Phe	Gly	Ser	Gly	Thr	Lys	Leu	Glu	Ile	Lys	Arg
			115				120						125			
	Ala	Asp	Ala	Ala	Pro	Thr	Val	Ser	Ile	Phe	Pro	Pro	Ser	Ser	Glu	Gln
		130					135					140				
	Leu	Thr	Ser	Gly	Gly	Ala	Ser	Val	Val	Cys	Phe	Leu	Asn	Asn	Phe	Tyr
20	145					150					155					160
	Pro	Lys	Asp	Ile	Asn	Val	Lys	Trp	Lys	Ile	Asp	Gly	Ser	Glu	Arg	Gln
				165						170					175	
	Asn	Gly	Val	Leu	Asn	Ser	Trp	Thr	Asp	Gln	Asp	Ser	Lys	Asp	Ser	Thr
			180						185					190		
25	Tyr	Ser	Met	Ser	Ser	Thr	Leu	Thr	Leu	Thr	Lys	Asp	Glu	Tyr	Glu	Arg
			195				200						205			
	His	Asn	Ser	Tyr	Thr	Cys	Glu	Ala	Thr	His	Lys	Thr	Ser	Thr	Ser	Pro
		210				215						220				
30	Ile	Val	Lys	Ser	Phe	Asn	Arg	Asn	Glu	Cys						
	225					230										

<210> 166

<211> 462

<212> PRT

35 <213> Artificial Sequence

<220>

<223> Hybrid of rat variable region and mouse constant region

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<400> 166

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	Val	Gln	Cys	Glu	Val	Gln	Leu	Val	Ala	Ser	Gly	Gly	Gly	Leu	Val	Lys
				20					25					30		
5	Pro	Gly	Ala	Ser	Leu	Lys	Leu	Ser	Cys	Val	Ala	Ser	Gly	Phe	Thr	Phe
			35				40						45			
	Ser	Asp	Tyr	Trp	Met	Ala	Trp	Val	Arg	Gln	Thr	Pro	Gly	Lys	Pro	Met
		50					55					60				
10	Glu	Tyr	Ile	Gly	Asp	Ile	Lys	Ser	Asp	Gly	Ser	Lys	Val	Asn	Tyr	Ala
	65					70					75					80
	Pro	Ser	Leu	Lys	Asn	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asn	Ala	Arg	Thr
					85					90					95	
	Thr	Leu	Tyr	Leu	Gln	Met	Ser	Asn	Val	Arg	Ser	Glu	Asp	Thr	Ala	Thr
				100					105					110		
15	Tyr	Tyr	Cys	Asn	Arg	Asp	Ile	Gly	Pro	Asp	Trp	Tyr	Phe	Asp	Phe	Trp
			115					120					125			
	Gly	Pro	Gly	Thr	Met	Val	Thr	Val	Ser	Ser	Ala	Lys	Thr	Thr	Pro	Pro
		130					135					140				
	Ser	Val	Tyr	Pro	Leu	Ala	Pro	Gly	Ser	Ala	Ala	Gln	Thr	Asn	Ser	Met
	145					150					155					160
20	Val	Thr	Leu	Gly	Cys	Leu	Val	Lys	Gly	Tyr	Phe	Pro	Glu	Pro	Val	Thr
					165					170					175	
	Val	Thr	Trp	Asn	Ser	Gly	Ser	Leu	Ser	Ser	Gly	Val	His	Thr	Phe	Pro
				180					185					190		
25	Ala	Val	Leu	Glu	Ser	Asp	Leu	Tyr	Thr	Leu	Ser	Ser	Ser	Val	Thr	Val
			195					200					205			
	Pro	Ser	Ser	Pro	Arg	Pro	Ser	Glu	Thr	Val	Thr	Cys	Asn	Val	Ala	His
		210					215					220				
	Pro	Ala	Ser	Ser	Thr	Lys	Val	Asp	Lys	Lys	Ile	Val	Pro	Arg	Asp	Cys
	225					230					235					240
30	Gly	Cys	Lys	Pro	Cys	Ile	Cys	Thr	Val	Pro	Glu	Val	Ser	Ser	Val	Phe
					245					250					255	
	Ile	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Val	Leu	Thr	Ile	Thr	Leu	Thr	Pro
				260					265					270		
	Lys	Val	Thr	Cys	Val	Val	Val	Asp	Ile	Ser	Lys	Asp	Asp	Pro	Glu	Val
			275					280					285			
35	Gln	Phe	Ser	Trp	Phe	Val	Asp	Asp	Val	Glu	Val	His	Thr	Ala	Gln	Thr
		290					295					300				
	Gln	Pro	Arg	Glu	Glu	Gln	Phe	Asn	Ser	Thr	Phe	Arg	Ser	Val	Ser	Glu
	305					310					315					320
	Leu	Pro	Ile	Met	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu	Phe	Lys	Cys
40																
					325					330					335	
	Arg	Val	Asn	Ser	Ala	Ala	Phe	Pro	Ala	Pro	Ile	Glu	Lys	Thr	Ile	Ser
				340					345					350		
45	Lys	Thr	Lys	Gly	Arg	Pro	Lys	Ala	Pro	Gln	Val	Tyr	Thr	Ile	Pro	Pro
			355					360					365			
	Pro	Lys	Glu	Gln	Met	Ala	Lys	Asp	Lys	Val	Ser	Leu	Thr	Cys	Met	Ile
		370					375					380				
	Thr	Asp	Phe	Phe	Pro	Glu	Asp	Ile	Thr	Val	Glu	Trp	Gln	Trp	Asn	Gly
	385					390					395					400
50	Gln	Pro	Ala	Glu	Asn	Tyr	Lys	Asn	Thr	Gln	Pro	Ile	Met	Asn	Thr	Asn
					405					410					415	
	Gly	Ser	Tyr	Phe	Val	Tyr	Ser	Lys	Leu	Asn	Val	Gln	Lys	Ser	Asn	Trp
				420					425					430		
	Glu	Ala	Gly	Asn	Thr	Phe	Thr	Cys	Ser	Val	Leu	His	Glu	Gly	Leu	His
			435					440					445			
55	Asn	His	His	Thr	Glu	Lys	Ser	Leu	Ser	His	Ser	Pro	Gly	Lys		
		450					455					460				

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<210> 167
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 <213> Rattus rattus

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<400> 167

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Met Gly Val Pro Thr Gln Leu Leu Gly Leu Leu Leu Leu Trp Ile Thr
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Asp Ala Ile Cys Asp Ile Gln Met Thr Gln Ser Pro Thr Ser Leu Ser
 20      25      30
Ala Ser Leu Gly Glu Thr Val Thr Ile Glu Cys Arg Ala Ser Glu Asp
 35      40      45
Ile Tyr Asn Gly Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ser Pro
 50      55      60
Gln Leu Leu Ile Tyr Asp Ser Asn Ser Leu His Thr Gly Val Pro Ser
 65      70      75      80
Arg Phe Ser Gly Arg Gly Ser Gly Thr Gln Tyr Ser Leu Arg Ile Asn
 85      90      95
Ser Leu Gln Ser Glu Asp Val Ala Ser Tyr Phe Cys Gln Gln Tyr Tyr
 100      105      110
Asp Tyr Pro Leu Thr Phe Gly Ser Gly Thr Lys Leu Glu Ile Lys Arg
 115      120      125
Ala Asp Ala Ala Pro Thr Val Ser Ile Phe Pro Pro Ser Ser Glu Gln
 130      135      140
Leu Thr Ser Gly Gly Ala Ser Val Val Cys Phe Leu Asn Asn Phe Tyr
 145      150      155      160
Pro Lys Asp Ile Asn Val Lys Trp Lys Ile Asp Gly Ser Glu Arg Gln
 165      170      175
Asn Gly Val Leu Asn Ser Trp Thr Asp Gln Asp Ser Lys Asp Ser Thr
 180      185      190
Tyr Ser Met Ser Ser Thr Leu Thr Leu Thr Lys Asp Glu Tyr Glu Arg
 195      200      205
His Asn Ser Tyr Thr Cys Glu Ala Thr His Lys Thr Ser Thr Ser Pro
 210      215      220
Ile Val Lys Ser Phe Asn Arg Asn Glu Cys
 225      230

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<210> 168
 <211> 462
 <212> PRT
 <213> Rattus rattus

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<400> 168

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	Met	Lys	Leu	Arg	Leu	Ser	Leu	Ile	Phe	Ile	Cys	Ala	Leu	Leu	Lys	Asp
	1				5					10					15	
	Val	Gln	Cys	Glu	Val	Gln	Leu	Val	Ala	Ser	Gly	Gly	Gly	Leu	Val	Lys
5				20					25					30		
	Pro	Gly	Ala	Ser	Leu	Lys	Leu	Ser	Cys	Val	Ala	Ser	Gly	Phe	Thr	Phe
			35					40					45			
	Ser	Asp	Tyr	Trp	Met	Ala	Trp	Val	Arg	Gln	Thr	Pro	Gly	Lys	Pro	Met
		50					55					60				
10	Glu	Tyr	Ile	Gly	Asp	Ile	Lys	Ser	Asp	Gly	Ser	Lys	Val	Asn	Tyr	Ala
	65					70					75					80
	Pro	Ser	Leu	Lys	Asn	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asn	Ala	Arg	Thr
					85					90					95	
	Thr	Leu	Tyr	Leu	Gln	Met	Ser	Asn	Val	Arg	Ser	Glu	Asp	Thr	Ala	Thr
				100					105					110		
15	Tyr	Tyr	Cys	Asn	Arg	Asp	Ile	Gly	Pro	Asp	Trp	Tyr	Phe	Asp	Phe	Trp
			115					120					125			
	Gly	Pro	Gly	Thr	Met	Val	Thr	Val	Ser	Ser	Ala	Lys	Thr	Thr	Pro	Pro
		130					135					140				
	Ser	Val	Tyr	Pro	Leu	Ala	Pro	Gly	Ser	Ala	Ala	Gln	Thr	Asn	Ser	Met
20		145				150					155					160
	Val	Thr	Leu	Gly	Cys	Leu	Val	Lys	Gly	Tyr	Phe	Pro	Glu	Pro	Val	Thr
				165						170					175	
	Val	Thr	Trp	Asn	Ser	Gly	Ser	Leu	Ser	Ser	Gly	Val	His	Thr	Phe	Pro
			180						185					190		
25	Ala	Val	Leu	Glu	Ser	Asp	Leu	Tyr	Thr	Leu	Ser	Ser	Ser	Val	Thr	Val
			195					200					205			
	Pro	Ser	Ser	Pro	Arg	Pro	Ser	Glu	Thr	Val	Thr	Cys	Asn	Val	Ala	His
		210					215					220				
	Pro	Ala	Ser	Ser	Thr	Lys	Val	Asp	Lys	Lys	Ile	Val	Pro	Arg	Asp	Cys
		225				230					235					240
30	Gly	Cys	Lys	Pro	Cys	Ile	Cys	Thr	Val	Pro	Glu	Val	Ser	Ser	Val	Phe
				245						250					255	
	Ile	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Val	Leu	Thr	Ile	Thr	Leu	Thr	Pro
			260						265					270		
	Lys	Val	Thr	Cys	Val	Val	Val	Asp	Ile	Ser	Lys	Asp	Asp	Pro	Glu	Val
			275					280					285			
35	Gln	Phe	Ser	Trp	Phe	Val	Asp	Asp	Val	Glu	Val	His	Thr	Ala	Gln	Thr
		290					295					300				
	Gln	Pro	Arg	Glu	Glu	Gln	Phe	Asn	Ser	Thr	Phe	Arg	Ser	Val	Ser	Glu
		305				310					315					320
	Leu	Pro	Ile	Met	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu	Phe	Lys	Cys
				325						330					335	
40	Arg	Val	Asn	Ser	Ala	Ala	Phe	Pro	Ala	Pro	Ile	Glu	Lys	Thr	Ile	Ser
			340						345					350		
	Lys	Thr	Lys	Gly	Arg	Pro	Lys	Ala	Pro	Gln	Val	Tyr	Thr	Ile	Pro	Pro
			355					360					365			
45	Pro	Lys	Glu	Gln	Met	Ala	Lys	Asp	Lys	Val	Ser	Leu	Thr	Cys	Met	Ile
		370					375					380				
	Thr	Asp	Phe	Phe	Pro	Glu	Asp	Ile	Thr	Val	Glu	Trp	Gln	Trp	Asn	Gly
		385				390					395					400
	Gln	Pro	Ala	Glu	Asn	Tyr	Lys	Asn	Thr	Gln	Pro	Ile	Met	Asn	Thr	Asn
				405						410					415	
50	Gly	Ser	Tyr	Phe	Val	Tyr	Ser	Lys	Leu	Asn	Val	Gln	Lys	Ser	Asn	Trp
				420					425					430		
	Glu	Ala	Gly	Asn	Thr	Phe	Thr	Cys	Ser	Val	Leu	His	Glu	Gly	Leu	His
			435					440					445			
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<210> 169

<211> 48

<212> DNA
<213> Artificial Sequence

<220>

5 <223> Oligonucleotide for mutagenesis for TLR3

<400> 169

gaagaactgg atatctttgc cgcttcacatc ttaaaaaaat tagagttg 48

10 <210> 170

<211> 44

<212> DNA

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15 <220>

<223> Oligonucleotide for mutagenesis for TLR3 variant

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gtcatctaca aaattaggaa ctgoggttca gctggaaaat ctcc 44

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<210> 171

<211> 45

<212> DNA

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<220>

<223> Oligonucleotide for mutagenesis for TLR3 variant

<400> 171

ctcataatgg cttgtcatct acagaattag gaactcaggt tcagc 45

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<210> 172

<211> 57

<212> DNA

35 <213> Artificial Sequence

<220>

<223> Oligonucleotide for mutagenesis for TLR3 variant

<400> 172

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<210> 173

<211> 50

45 <212> DNA

<213> Artificial Sequence

<220>

<223> Oligonucleotide for mutagenesis for TLR3 variant

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<400> 173

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<210> 174

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<212> DNA

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15 <400> 175
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<210> 176
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 20 <212> DNA
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25 <400> 176
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<210> 177
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 30 <212> DNA
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<220>
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35 <400> 177
 gtcttgagaa actagaaatt ctcaagttgc agcataacaa ctagcac 48

<210> 178
 <211> 46
 40 <212> DNA
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<220>
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45 <400> 178
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50 <210> 179
 <211> 43
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55 <220>
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<400> 179
 ctaaagtcac tgaacctca ggagaatctc ataacatccg ttg 43

5
 <210> 180
 <211> 47
 <212> DNA
 <213> Artificial Sequence

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 <223> Oligonucleotide for mutagenesis for TLR3 variant

<400> 180
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 <210> 181
 <211> 37
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 <210> 182
 <211> 46
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<400> 182
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 <210> 183
 <211> 46
 <212> DNA
 <213> Artificial Sequence

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<400> 183
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 <210> 184
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 <212> DNA
 <213> Artificial Sequence

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<400> 184
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<210> 185
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 <400> 185
 10 ctagaaattc tgcatttgca ggctaacaac ttagcacggc tctg 44
 <210> 186
 <211> 46
 <212> DNA
 15 <213> Artificial Sequence
 <220>
 <223> Oligonucleotide for mutagenesis for TLR3 variant
 20 <400> 186
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 <210> 187
 <211> 50
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 Xaa Ile Xaa Xaa Arg Ser Xaa Trp Tyr Asn Asp Tyr Ala Val Ser Val
 20 1 5 10 15
 Lys Ser

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Xaa Ser Tyr Asp Xaa Pro Xaa Xaa Xaa Val
1 5 10

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Lys Ser

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 1 5 10 15
 Gly
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Thr	Ala	Arg	Ile	Ser	Cys	Ser	Gly	Asp	Ala	Leu	Gly	Gly	Tyr	Phe	Val
			20					25					30		
Ser	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Gln	Ala	Pro	Val	Leu	Val	Ile	Tyr
		35					40					45			
Asp	Asp	Asp	Asn	Arg	Pro	Ser	Gly	Ile	Pro	Glu	Arg	Phe	Ser	Gly	Ser
	50					55					60				
Asn	Ser	Gly	Asn	Thr	Ala	Thr	Leu	Thr	Ile	Ser	Gly	Thr	Gln	Ala	Glu
65					70					75					80
Asp	Glu	Ala	Asp	Tyr	Tyr	Cys	Xaa	Ser	Tyr	Asp	Xaa	Xaa	Xaa	Xaa	Thr
				85					90					95	
Val	Phe	Gly	Gly	Gly	Thr	Lys	Leu	Thr	Val	Leu					
			100					105							

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<222> (58)

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      Thr Leu Ser Leu Thr Cys Ala Ile Ser Gly Asp Ser Val Ser Thr Arg
        20
      Ser Ala Ala Trp Gly Trp Ile Arg Gln Ser Pro Gly Arg Gly Leu Glu
15      35          40          45
      Trp Leu Gly Xaa Ile Xaa Xaa Arg Ser Xaa Trp Tyr Asn Asp Tyr Ala
        50          55          60
      Val Ser Val Lys Ser Arg Ile Thr Ile Asn Pro Asp Thr Ser Lys Asn
        65          70          75          80
      Gln Phe Ser Leu Gln Leu Asn Ser Val Thr Pro Glu Asp Thr Ala Val
20      85          90          95
      Tyr Tyr Cys Ala Arg His Thr Tyr Pro Tyr Leu Ser Phe Asp Val Trp
        100          105          110
      Gly Gln Gly Thr Leu Val Thr Val Ser Ser
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	Thr	Ala	Arg	Ile	Ser	Cys	Ser	Gly	Asp	Asn	Ile	Gly	Ser	Tyr	Tyr	Val
				20					25					30		
	His	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Gln	Ala	Pro	Val	Leu	Val	Ile	Tyr
				35					40					45		
10	Glu	Asp	Ser	Glu	Arg	Pro	Ser	Gly	Ile	Pro	Glu	Arg	Phe	Ser	Gly	Ser
		50					55					60				
	Asn	Ser	Gly	Asn	Thr	Ala	Thr	Leu	Thr	Ile	Ser	Gly	Thr	Gln	Ala	Glu
	65					70					75					80
	Asp	Glu	Ala	Asp	Tyr	Cys	Xaa	Ser	Tyr	Asp	Xaa	Pro	Xaa	Xaa	Xaa	
				85					90					95		
15	Val	Phe	Gly	Gly	Gly	Thr	Lys	Leu	Thr	Val	Leu					
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<223> Wherein Xaa can be Val or Leu

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	1				5					10					15	
	Thr	Leu	Ser	Leu	Thr	Cys	Ala	Ile	Ser	Gly	Asp	Ser	Val	Ser	Ser	Asn

50

55

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				20					25					30		
	Ser	Ala	Ala	Trp	Gly	Trp	Ile	Arg	Gln	Ser	Pro	Gly	Arg	Gly	Leu	Glu
			35					40					45			
5	Trp	Leu	Gly	Ile	Ile	Gln	Xaa	Arg	Ser	Lys	Trp	Tyr	Asn	Xaa	Tyr	Ala
		50					55					60				
	Xaa	Ser	Val	Lys	Ser	Arg	Ile	Thr	Ile	Asn	Pro	Asp	Thr	Ser	Lys	Asn
	65					70					75				80	
	Gln	Phe	Ser	Leu	Gln	Leu	Asn	Ser	Val	Thr	Pro	Glu	Asp	Thr	Ala	Val
				85						90					95	
10	Tyr	Tyr	Cys	Ala	Arg	Tyr	Ser	Tyr	Pro	Phe	Tyr	Ser	Ile	Asp	Tyr	Trp
				100					105					110		
	Gly	Gln	Gly	Thr	Leu	Val	Thr	Val	Ser	Ser						
			115					120								

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	Asp	Arg	Val	Thr	Ile	Thr	Cys	Arg	Ala	Ser	Gln	Ser	Ile	Gly	Leu	Tyr
				20					25					30		
5	Leu	Ala	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Lys	Ala	Pro	Lys	Leu	Leu	Ile
		35					40					45				
	Tyr	Ala	Ala	Ser	Ser	Leu	Gln	Ser	Gly	Val	Pro	Ser	Arg	Phe	Ser	Gly
	50						55					60				
10																
	Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Thr	Ile	Ser	Ser	Leu	Gln	Pro
	65					70					75					80
	Glu	Asp	Phe	Ala	Thr	Tyr	Tyr	Cys	Gln	Gln	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa
				85						90					95	
	Thr	Phe	Gly	Gln	Gly	Thr	Lys	Val	Glu	Ile	Lys					
15				100					105							

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	Ser	Leu	Lys	Ile	Ser	Cys	Lys	Gly	Ser	Gly	Tyr	Ser	Phe	Thr	Asn	Tyr
				20					25					30		
40	Trp	Val	Gly	Trp	Val	Arg	Gln	Met	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Met
		35					40						45			
	Gly	Xaa	Ile	Asp	Pro	Ser	Asp	Ser	Tyr	Thr	Asn	Tyr	Xaa	Pro	Ser	Phe
	50					55					60					
45	Gln	Gly	Gln	Val	Thr	Ile	Ser	Ala	Asp	Lys	Ser	Ile	Ser	Thr	Ala	Tyr
	65					70					75					80
	Leu	Gln	Trp	Ser	Ser	Leu	Lys	Ala	Ser	Asp	Thr	Ala	Met	Tyr	Tyr	Cys
				85						90					95	
	Ala	Arg	Glu	Leu	Tyr	Gln	Gly	Tyr	Met	Asp	Thr	Phe	Asp	Ser	Trp	Gly
				100					105					110		
50	Gln	Gly	Thr	Leu	Val	Thr	Val	Ser	Ser							
			115					120								

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<223> Full length consensus light chain, family 17

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Thr	Ala	Arg	Ile	Ser	Cys	Ser	Gly	Asp	Ala	Leu	Gly	Gly	Tyr	Phe	Val
			20					25					30		
Ser	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Gln	Ala	Pro	Val	Leu	Val	Ile	Tyr
		35					40					45			
Asp	Asp	Asp	Asn	Arg	Pro	Ser	Gly	Ile	Pro	Glu	Arg	Phe	Ser	Gly	Ser
	50					55					60				
Asn	Ser	Gly	Asn	Thr	Ala	Thr	Leu	Thr	Ile	Ser	Gly	Thr	Gln	Ala	Glu
65				70						75				80	
Asp	Glu	Ala	Asp	Tyr	Tyr	Cys	Xaa	Ser	Tyr	Asp	Xaa	Xaa	Xaa	Xaa	Thr
			85						90					95	
Val	Phe	Gly	Gly	Gly	Thr	Lys	Leu	Thr	Val	Leu	Arg	Thr	Val	Ala	Ala
			100						105				110		
Pro	Ser	Val	Phe	Ile	Phe	Pro	Pro	Ser	Asp	Glu	Gln	Leu	Lys	Ser	Gly
		115						120				125			
Thr	Ala	Ser	Val	Val	Cys	Leu	Leu	Asn	Asn	Phe	Tyr	Pro	Arg	Glu	Ala
	130				135						140				
Lys	Val	Gln	Trp	Lys	Val	Asp	Asn	Ala	Leu	Gln	Ser	Gly	Asn	Ser	Gln
145				150						155				160	
Glu	Ser	Val	Thr	Glu	Gln	Asp	Ser	Lys	Asp	Ser	Thr	Tyr	Ser	Leu	Ser
			165						170					175	
Ser	Thr	Leu	Thr	Leu	Ser	Lys	Ala	Asp	Tyr	Glu	Lys	His	Lys	Val	Tyr
		180						185					190		
Ala	Cys	Glu	Val	Thr	His	Gln	Gly	Leu	Ser	Ser	Pro	Val	Thr	Lys	Ser
		195					200					205			
Phe	Asn	Arg	Gly	Glu	Cys										
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	1				5					10					15	
	Thr	Leu	Ser	Leu	Thr	Cys	Ala	Ile	Ser	Gly	Asp	Ser	Val	Ser	Thr	Arg
5				20					25					30		
	Ser	Ala	Ala	Trp	Gly	Trp	Ile	Arg	Gln	Ser	Pro	Gly	Arg	Gly	Leu	Glu
		35						40					45			
	Trp	Leu	Gly	Xaa	Ile	Xaa	Xaa	Arg	Ser	Xaa	Trp	Tyr	Asn	Asp	Tyr	Ala
	50					55						60				
	Val	Ser	Val	Lys	Ser	Arg	Ile	Thr	Ile	Asn	Pro	Asp	Thr	Ser	Lys	Asn
10	65					70					75					80
	Gln	Phe	Ser	Leu	Gln	Leu	Asn	Ser	Val	Thr	Pro	Glu	Asp	Thr	Ala	Val
				85						90					95	
	Tyr	Tyr	Cys	Ala	Arg	His	Thr	Tyr	Pro	Tyr	Leu	Ser	Phe	Asp	Val	Trp
				100					105					110		
15	Gly	Gln	Gly	Thr	Leu	Val	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro
		115						120					125			
	Ser	Val	Phe	Pro	Leu	Ala	Pro	Cys	Ser	Arg	Ser	Thr	Ser	Glu	Ser	Thr
		130					135						140			
	Ala	Ala	Leu	Gly	Cys	Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr
	145					150					155					160
20	Val	Ser	Trp	Asn	Ser	Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro
				165						170					175	
	Ala	Val	Leu	Gln	Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr
			180					185						190		
	Val	Pro	Ser	Ser	Ser	Leu	Gly	Thr	Lys	Thr	Tyr	Thr	Cys	Asn	Val	Asp
25			195					200					205			
	His	Lys	Pro	Ser	Asn	Thr	Lys	Val	Asp	Lys	Arg	Val	Glu	Ser	Lys	Tyr
		210					215					220				
	Gly	Pro	Pro	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Ala	Ala	Gly	Gly	Pro
	225					230					235					240
30	Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser
				245						250					255	
	Arg	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	Gln	Glu	Asp
			260					265						270		
	Pro	Glu	Val	Gln	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn
		275						280					285			
35	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Phe	Asn	Ser	Thr	Tyr	Arg	Val
		290					295					300				
	Val	Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu
	305					310					315					320
	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Gly	Leu	Pro	Ser	Ser	Ile	Glu	Lys
				325						330					335	
40	Thr	Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr
			340					345						350		
	Leu	Pro	Pro	Ser	Gln	Glu	Glu	Met	Thr	Lys	Asn	Gln	Val	Ser	Leu	Thr
		355					360						365			
45	Cys	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu
		370					375					380				
	Ser	Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Val	Leu
	385					390					395					400
50	Asp	Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser	Arg	Leu	Thr	Val	Asp	Lys
				405						410					415	
	Ser	Arg	Trp	Gln	Glu	Gly	Asn	Val	Phe	Ser	Cys	Ser	Val	Met	His	Glu
			420						425					430		
	Ala	Leu	His	Asn	His	Tyr	Thr	Gln	Lys	Ser	Leu	Ser	Leu	Ser	Leu	Gly
			435					440					445			
55	Lys															

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 $\langle 220 \rangle$

<221> misc feature

<222> (92)

<223> Wherein Xaa can be Thr, Glu or Asp

 $\langle 220 \rangle$

<221> misc feature

<222> (94)

<223> Wherein Xaa can be Val or Asn

 $\langle 220 \rangle$

<221> misc_feature

<222> (95)

<223> Wherein Xaa can be Tyr or Phe

$\langle 220 \rangle$

<221> misc_feature

<222> (96)

<223> Wherein Xaa can be Ser, Asn or Gln

<400> 205

Asp Ile Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ala Pro Gly Gln

1 5 10 15

Thr Ala Arg Ile Ser Cys Ser Gly Asp Asn Ile Gly Ser Tyr Tyr Val

20 25 30

His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr

35 40 45

Glu Asp Ser Glu Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser

50 55 60

Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Glu

65 70 75 80

Asp Glu Ala Asp Tyr Tyr Cys Xaa Ser Tyr Asp Xaa Pro Xaa Xaa Xaa

85 90 95

Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Arg Thr Val Ala Ala

100 105 110

Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly

115	120	125
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	Thr	Ala	Ser	Val	Val	Cys	Leu	Leu	Asn	Asn	Phe	Tyr	Pro	Arg	Glu	Ala
		130					135					140				
	Lys	Val	Gln	Trp	Lys	Val	Asp	Asn	Ala	Leu	Gln	Ser	Gly	Asn	Ser	Gln
5	145				150					155						160
	Glu	Ser	Val	Thr	Glu	Gln	Asp	Ser	Lys	Asp	Ser	Thr	Tyr	Ser	Leu	Ser
				165					170						175	
	Ser	Thr	Leu	Thr	Leu	Ser	Lys	Ala	Asp	Tyr	Glu	Lys	His	Lys	Val	Tyr
			180					185						190		
10	Ala	Cys	Glu	Val	Thr	His	Gln	Gly	Leu	Ser	Ser	Pro	Val	Thr	Lys	Ser
		195						200					205			
	Phe	Asn	Arg	Gly	Glu	Cys										
		210														

15 <210> 206
 <211> 449
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20 <220>
 <223> Full length consensus heavy chain family 18A and 18B

25 <220>
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 <222> (55)
 <223> Wherein Xaa can be Lys, Thr or Ile

30 <220>
 <221> misc_feature
 <222> (62)
 <223> Wherein Xaa can be Asn or Asp

35 <220>
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 <222> (65)
 <223> Wherein Xaa can be Val or Leu

<400> 206

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45

50

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	Gln	Val	Glu	Leu	Gln	Gln	Ser	Gly	Pro	Gly	Leu	Val	Lys	Pro	Ser	Gln
	1				5					10					15	
	Thr	Leu	Ser	Leu	Thr	Cys	Ala	Ile	Ser	Gly	Asp	Ser	Val	Ser	Ser	Asn
5				20					25					30		
	Ser	Ala	Ala	Trp	Gly	Trp	Ile	Arg	Gln	Ser	Pro	Gly	Arg	Gly	Leu	Glu
		35						40					45			
	Trp	Leu	Gly	Ile	Ile	Gln	Xaa	Arg	Ser	Lys	Trp	Tyr	Asn	Xaa	Tyr	Ala
	50						55					60				
10	Xaa	Ser	Val	Lys	Ser	Arg	Ile	Thr	Ile	Asn	Pro	Asp	Thr	Ser	Lys	Asn
	65					70					75					80
	Gln	Phe	Ser	Leu	Gln	Leu	Asn	Ser	Val	Thr	Pro	Glu	Asp	Thr	Ala	Val
					85					90					95	
	Tyr	Tyr	Cys	Ala	Arg	Tyr	Ser	Tyr	Pro	Phe	Tyr	Ser	Ile	Asp	Tyr	Trp
				100					105					110		
15	Gly	Gln	Gly	Thr	Leu	Val	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro
			115					120						125		
	Ser	Val	Phe	Pro	Leu	Ala	Pro	Cys	Ser	Arg	Ser	Thr	Ser	Glu	Ser	Thr
		130					135					140				
	Ala	Ala	Leu	Gly	Cys	Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr
	145					150					155					160
20	Val	Ser	Trp	Asn	Ser	Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro
				165						170					175	
	Ala	Val	Leu	Gln	Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr
25				180					185				190			
	Val	Pro	Ser	Ser	Ser	Leu	Gly	Thr	Lys	Thr	Tyr	Thr	Cys	Asn	Val	Asp
			195					200					205			
	His	Lys	Pro	Ser	Asn	Thr	Lys	Val	Asp	Lys	Arg	Val	Glu	Ser	Lys	Tyr
		210					215					220				
30	Gly	Pro	Pro	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Ala	Ala	Gly	Gly	Pro
	225				230						235					240
	Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser
				245						250					255	
	Arg	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	Gln	Glu	Asp
			260					265						270		
35	Pro	Glu	Val	Gln	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn
		275						280					285			
	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Gln	Phe	Asn	Ser	Thr	Tyr	Arg	Val	
		290					295				300					
	Val	Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu
	305				310						315					320
40	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Gly	Leu	Pro	Ser	Ser	Ile	Glu	Lys
				325						330					335	
	Thr	Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr
				340					345					350		
45	Leu	Pro	Pro	Ser	Gln	Glu	Glu	Met	Thr	Lys	Asn	Gln	Val	Ser	Leu	Thr
			355					360					365			
	Cys	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu
		370					375					380				
	Ser	Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Val	Leu
	385				390						395					400
50	Asp	Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser	Arg	Leu	Thr	Val	Asp	Lys
				405						410					415	
	Ser	Arg	Trp	Gln	Glu	Gly	Asn	Val	Phe	Ser	Cys	Ser	Val	Met	His	Glu
				420					425					430		
	Ala	Leu	His	Asn	His	Tyr	Thr	Gln	Lys	Ser	Leu	Ser	Leu	Ser	Leu	Gly
			435					440					445			
55	Lys															

<210> 207

<211> 214

<212> PRT
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<220>

5 <223> Full length consensus light chain family 19

<220>

<221> misc_feature

<222> (91)

10 <223> Wherein Xaa can be Tyr, Gly or Ala

<220>

<221> misc_feature

<222> (92)

15 <223> Wherein Xaa can be Gly, Glu or Asn

<220>

<221> misc_feature

<222> (93)

20 <223> Wherein Xaa can be Ser or Thr

<220>

<221> misc_feature

<222> (94)

25 <223> Wherein Xaa can be Val, Ile or Leu

<220>

<221> misc_feature

<222> (95)

30 <223> Wherein Xaa can be Ser or Leu

<220>

<221> misc_feature

<222> (96)

35 <223> Wherein Xaa can be Ile, Ser, Pro or Tyr

<400> 207

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	Asp	Ile	Gln	Met	Thr	Gln	Ser	Pro	Ser	Ser	Leu	Ser	Ala	Ser	Val	Gly
	1				5					10					15	
	Asp	Arg	Val	Thr	Ile	Thr	Cys	Arg	Ala	Ser	Gln	Ser	Ile	Gly	Leu	Tyr
				20					25					30		
5	Leu	Ala	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Lys	Ala	Pro	Lys	Leu	Leu	Ile
			35				40						45			
	Tyr	Ala	Ala	Ser	Ser	Leu	Gln	Ser	Gly	Val	Pro	Ser	Arg	Phe	Ser	Gly
		50					55					60				
	Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Thr	Ile	Ser	Ser	Leu	Gln	Pro
10		65				70					75					80
	Glu	Asp	Phe	Ala	Thr	Tyr	Tyr	Cys	Gln	Gln	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa
					85					90					95	
	Thr	Phe	Gly	Gln	Gly	Thr	Lys	Val	Glu	Ile	Lys	Arg	Thr	Val	Ala	Ala
				100					105					110		
15	Pro	Ser	Val	Phe	Ile	Phe	Pro	Pro	Ser	Asp	Glu	Gln	Leu	Lys	Ser	Gly
			115				120						125			
	Thr	Ala	Ser	Val	Val	Cys	Leu	Leu	Asn	Asn	Phe	Tyr	Pro	Arg	Glu	Ala
		130					135					140				
	Lys	Val	Gln	Trp	Lys	Val	Asp	Asn	Ala	Leu	Gln	Ser	Gly	Asn	Ser	Gln
		145				150					155					160
20	Glu	Ser	Val	Thr	Glu	Gln	Asp	Ser	Lys	Asp	Ser	Thr	Tyr	Ser	Leu	Ser
					165					170					175	
	Ser	Thr	Leu	Thr	Leu	Ser	Lys	Ala	Asp	Tyr	Glu	Lys	His	Lys	Val	Tyr
				180					185					190		
	Ala	Cys	Glu	Val	Thr	His	Gln	Gly	Leu	Ser	Ser	Pro	Val	Thr	Lys	Ser
25			195					200					205			
	Phe	Asn	Arg	Gly	Glu	Cys										
				210												

30 <210> 208
 <211> 448
 <212> PRT
 <213> Artificial Sequence

35 <220>
 <223> Full length consensus heavy chain family 19

40 <220>
 <221> misc_feature
 <222> (50)
 <223> Wherein Xaa can be Phe or Arg

45 <220>
 <221> misc_feature
 <222> (61)
 <223>

<400> 208

50

55

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	Gln	Val	Glu	Leu	Val	Gln	Ser	Gly	Ala	Glu	Val	Lys	Lys	Pro	Gly	Glu
	1				5					10					15	
	Ser	Leu	Lys	Ile	Ser	Cys	Lys	Gly	Ser	Gly	Tyr	Ser	Phe	Thr	Asn	Tyr
				20				25						30		
5	Trp	Val	Gly	Trp	Val	Arg	Gln	Met	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Met
			35					40					45			
	Gly	Xaa	Ile	Asp	Pro	Ser	Asp	Ser	Tyr	Thr	Asn	Tyr	Xaa	Pro	Ser	Phe
		50					55					60				
10	Gln	Gly	Gln	Val	Thr	Ile	Ser	Ala	Asp	Lys	Ser	Ile	Ser	Thr	Ala	Tyr
	65					70					75					80
	Leu	Gln	Trp	Ser	Ser	Leu	Lys	Ala	Ser	Asp	Thr	Ala	Met	Tyr	Tyr	Cys
					85					90					95	
	Ala	Arg	Glu	Leu	Tyr	Gln	Gly	Tyr	Met	Asp	Thr	Phe	Asp	Ser	Trp	Gly
				100					105					110		
15	Gln	Gly	Thr	Leu	Val	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro	Ser
			115					120					125			
	Val	Phe	Pro	Leu	Ala	Pro	Cys	Ser	Arg	Ser	Thr	Ser	Glu	Ser	Thr	Ala
		130					135					140				
	Ala	Leu	Gly	Cys	Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val
	145					150					155					160
20	Ser	Trp	Asn	Ser	Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro	Ala
					165					170					175	
	Val	Leu	Gln	Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val
				180				185						190		
25	Pro	Ser	Ser	Ser	Leu	Gly	Thr	Lys	Thr	Tyr	Thr	Cys	Asn	Val	Asp	His
			195					200					205			
	Lys	Pro	Ser	Asn	Thr	Lys	Val	Asp	Lys	Arg	Val	Glu	Ser	Lys	Tyr	Gly
		210					215					220				
	Pro	Pro	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Ala	Ala	Gly	Gly	Pro	Ser
	225					230					235					240
30	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser	Arg
					245					250					255	
	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	Gln	Glu	Asp	Pro
				260					265					270		
	Glu	Val	Gln	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn	Ala
			275					280					285			
35	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Phe	Asn	Ser	Thr	Tyr	Arg	Val	Val
		290					295					300				
	Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu	Tyr
	305					310					315					320
	Lys	Cys	Lys	Val	Ser	Asn	Lys	Gly	Leu	Pro	Ser	Ser	Ile	Glu	Lys	Thr
					325					330					335	
40	Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr	Leu
				340					345					350		
	Pro	Pro	Ser	Gln	Glu	Glu	Met	Thr	Lys	Asn	Gln	Val	Ser	Leu	Thr	Cys
				355				360					365			
45	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu	Ser
		370					375					380				
	Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Val	Leu	Asp
	385					390					395					400
	Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser	Arg	Leu	Thr	Val	Asp	Lys	Ser
					405					410					415	
50	Arg	Trp	Gln	Glu	Gly	Asn	Val	Phe	Ser	Cys	Ser	Val	Met	His	Glu	Ala
				420					425					430		
	Leu	His	Asn	His	Tyr	Thr	Gln	Lys	Ser	Leu	Ser	Leu	Ser	Leu	Gly	Lys
			435					440					445			

55 <210> 209
 <211> 108
 <212> PRT
 <213> Artificial Sequence

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<220>

<223> QSV Variant of candidate 9 variable light chain

<400> 209

5

10

15

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25

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35

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Gln Ser Val Leu Thr Gln Pro Pro Ser Val Ser Val Ala Pro Gly Gln
 1      5      10      15
Thr Ala Arg Ile Ser Cys Ser Gly Asp Asn Ile Gly Ser Tyr Tyr Val
      20      25      30
His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr
      35      40      45
Glu Asp Ser Glu Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
      50      55      60
Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Glu
65      70      75      80
Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Ser Gln Phe Ser Phe
      85      90      95
Gly Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
      100      105

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<210> 210

<211> 107

<212> PRT

<213> Artificial Sequence

<220>

<223> QSV variant of candidate 10 variable light chain

<400> 210

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Gln Ser Val Leu Thr Gln Pro Pro Ser Val Ser Val Ala Pro Gly Gln
 1      5      10      15
Thr Ala Arg Ile Ser Cys Ser Gly Asp Asn Ile Gly Ser Tyr Tyr Val
      20      25      30
His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr
      35      40      45
Glu Asp Ser Glu Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
      50      55      60
Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Glu
65      70      75      80
Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Thr Pro Val Tyr Ser
      85      90      95
Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
      100      105

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<210> 211

<211> 107

<212> PRT

<213> Artificial Sequence

<220>

<223> QSV variant of candidate 12 variable light chain

<400> 211

EP 2 350 304 B1

	Gln	Ser	Val	Leu	Thr	Gln	Pro	Pro	Ser	Val	Ser	Val	Ala	Pro	Gly	Gln
	1				5					10					15	
	Thr	Ala	Arg	Ile	Ser	Cys	Ser	Gly	Asp	Asn	Ile	Gly	Ser	Tyr	Tyr	Val
				20					25					30		
5	His	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Gln	Ala	Pro	Val	Leu	Val	Ile	Tyr
			35					40					45			
	Glu	Asp	Ser	Glu	Arg	Pro	Ser	Gly	Ile	Pro	Glu	Arg	Phe	Ser	Gly	Ser
		50					55					60				
10																
	Asn	Ser	Gly	Asn	Thr	Ala	Thr	Leu	Thr	Ile	Ser	Gly	Thr	Gln	Ala	Glu
	65					70					75					80
	Asp	Glu	Ala	Asp	Tyr	Tyr	Cys	Ser	Ser	Tyr	Asp	Asp	Pro	Asn	Phe	Gln
					85					90					95	
	Val	Phe	Gly	Gly	Gly	Thr	Lys	Leu	Thr	Val	Leu					
15				100					105							

<210> 212

<211> 122

<212> PRT

20 <213> Artificial Sequence

<220>

<223> QVQ variant of candidate 9 variable heavy chain

25 <400> 212

	Gln	Val	Gln	Leu	Gln	Gln	Ser	Gly	Pro	Gly	Leu	Val	Lys	Pro	Ser	Gln
	1				5					10					15	
	Thr	Leu	Ser	Leu	Thr	Cys	Ala	Ile	Ser	Gly	Asp	Ser	Val	Ser	Ser	Asn
				20					25					30		
30	Ser	Ala	Ala	Trp	Gly	Trp	Ile	Arg	Gln	Ser	Pro	Gly	Arg	Gly	Leu	Glu
			35					40					45			
	Trp	Leu	Gly	Ile	Ile	Gln	Ile	Arg	Ser	Lys	Trp	Tyr	Asn	Asp	Tyr	Ala
			50				55					60				
35	Leu	Ser	Val	Lys	Ser	Arg	Ile	Thr	Ile	Asn	Pro	Asp	Thr	Ser	Lys	Asn
						70					75					80
	Gln	Phe	Ser	Leu	Gln	Leu	Asn	Ser	Val	Thr	Pro	Glu	Asp	Thr	Ala	Val
					85					90					95	
	Tyr	Tyr	Cys	Ala	Arg	Tyr	Ser	Tyr	Pro	Phe	Tyr	Ser	Ile	Asp	Tyr	Trp
				100					105					110		
40	Gly	Gln	Gly	Thr	Leu	Val	Thr	Val	Ser	Ser						
			115					120								

<210> 213

<211> 122

45 <212> PRT

<213> Artificial Sequence

<220>

<223> QVQ variant of candidate 10 variable heavy chain

50 <400> 213

55

EP 2 350 304 B1

	Gln	Val	Gln	Leu	Gln	Gln	Ser	Gly	Pro	Gly	Leu	Val	Lys	Pro	Ser	Gln
	1				5					10					15	
	Thr	Leu	Ser	Leu	Thr	Cys	Ala	Ile	Ser	Gly	Asp	Ser	Val	Ser	Ser	Asn
				20					25					30		
5	Ser	Ala	Ala	Trp	Gly	Trp	Ile	Arg	Gln	Ser	Pro	Gly	Arg	Gly	Leu	Glu
			35					40					45			
	Trp	Leu	Gly	Ile	Ile	Gln	Lys	Arg	Ser	Lys	Trp	Tyr	Asn	Asn	Tyr	Ala
	50						55					60				
	Val	Ser	Val	Lys	Ser	Arg	Ile	Thr	Ile	Asn	Pro	Asp	Thr	Ser	Lys	Asn
10	65					70					75					80
	Gln	Phe	Ser	Leu	Gln	Leu	Asn	Ser	Val	Thr	Pro	Glu	Asp	Thr	Ala	Val
					85					90					95	
	Tyr	Tyr	Cys	Ala	Arg	Tyr	Ser	Tyr	Pro	Phe	Tyr	Ser	Ile	Asp	Tyr	Trp
				100					105					110		
	Gly	Gln	Gly	Thr	Leu	Val	Thr	Val	Ser	Ser						
15			115					120								

<210> 214

<211> 122

<212> PRT

20 <213> Artificial Sequence

<220>

<223> QVQ variant of candidate 12 variable heavy chain

25 <400> 214

	Gln	Val	Gln	Leu	Gln	Gln	Ser	Gly	Pro	Gly	Leu	Val	Lys	Pro	Ser	Gln
	1				5					10					15	
	Thr	Leu	Ser	Leu	Thr	Cys	Ala	Ile	Ser	Gly	Asp	Ser	Val	Ser	Ser	Asn
				20					25					30		
30	Ser	Ala	Ala	Trp	Gly	Trp	Ile	Arg	Gln	Ser	Pro	Gly	Arg	Gly	Leu	Glu
			35					40					45			
	Trp	Leu	Gly	Ile	Ile	Gln	Lys	Arg	Ser	Lys	Trp	Tyr	Asn	Asn	Tyr	Ala
	50						55					60				
	Val	Ser	Val	Lys	Ser	Arg	Ile	Thr	Ile	Asn	Pro	Asp	Thr	Ser	Lys	Asn
35	65					70					75					80
	Gln	Phe	Ser	Leu	Gln	Leu	Asn	Ser	Val	Thr	Pro	Glu	Asp	Thr	Ala	Val
					85					90					95	
	Tyr	Tyr	Cys	Ala	Arg	Tyr	Ser	Tyr	Pro	Phe	Tyr	Ser	Ile	Asp	Tyr	Trp
				100					105					110		
40	Gly	Gln	Gly	Thr	Leu	Val	Thr	Val	Ser	Ser						
			115					120								

<210> 215

<211> 121

45 <212> PRT

<213> Artificial Sequence

<220>

<223> EVQ variant of candidate 14

50 <400> 215

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EP 2 350 304 B1

	Glu	Val	Gln	Leu	Val	Gln	Ser	Gly	Ala	Glu	Val	Lys	Lys	Pro	Gly	Glu
	1				5					10					15	
	Ser	Leu	Lys	Ile	Ser	Cys	Lys	Gly	Ser	Gly	Tyr	Ser	Phe	Thr	Asn	Tyr
				20					25					30		
5	Trp	Val	Gly	Trp	Val	Arg	Gln	Met	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Met
			35					40					45			
	Gly	Phe	Ile	Asp	Pro	Ser	Asp	Ser	Tyr	Thr	Asn	Tyr	Ala	Pro	Ser	Phe
		50					55					60				
	Gln	Gly	Gln	Val	Thr	Ile	Ser	Ala	Asp	Lys	Ser	Ile	Ser	Thr	Ala	Tyr
10		65				70					75					80
	Leu	Gln	Trp	Ser	Ser	Leu	Lys	Ala	Ser	Asp	Thr	Ala	Met	Tyr	Tyr	Cys
					85					90					95	
	Ala	Arg	Glu	Leu	Tyr	Gln	Gly	Tyr	Met	Asp	Thr	Phe	Asp	Ser	Trp	Gly
				100					105					110		
15	Gln	Gly	Thr	Leu	Val	Thr	Val	Ser	Ser							
			115					120								

<210> 216

<211> 121

<212> PRT

20 <213> Artificial Sequence

<220>

<223> EVQ variant of candidate 15

25 <400> 216

	Glu	Val	Gln	Leu	Val	Gln	Ser	Gly	Ala	Glu	Val	Lys	Lys	Pro	Gly	Glu
	1				5					10					15	
	Ser	Leu	Lys	Ile	Ser	Cys	Lys	Gly	Ser	Gly	Tyr	Ser	Phe	Thr	Asn	Tyr
				20					25					30		
35	Trp	Val	Gly	Trp	Val	Arg	Gln	Met	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Met
			35					40					45			
	Gly	Phe	Ile	Asp	Pro	Ser	Asp	Ser	Tyr	Thr	Asn	Tyr	Ala	Pro	Ser	Phe
		50					55					60				
	Gln	Gly	Gln	Val	Thr	Ile	Ser	Ala	Asp	Lys	Ser	Ile	Ser	Thr	Ala	Tyr
		65				70					75					80
40	Leu	Gln	Trp	Ser	Ser	Leu	Lys	Ala	Ser	Asp	Thr	Ala	Met	Tyr	Tyr	Cys
					85					90					95	
	Ala	Arg	Glu	Leu	Tyr	Gln	Gly	Tyr	Met	Asp	Thr	Phe	Asp	Ser	Trp	Gly
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<210> 217

<211> 2712

<212> DNA

50 <213> Macaca fascicularis

<400> 217

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35	cttctcatcc	actttgaggg	ctggaggata	tctttttact	ggaatgtttc	agtacatcga	2220
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<210> 218

<211> 449

<212> PRT

50 <213> Artificial Sequence

<220>

<223> Candidate 9EVQ full length heavy chain with S229P, F235A/L236A

55 <400> 218

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	Thr	Leu	Ser	Leu	Thr	Cys	Ala	Ile	Ser	Gly	Asp	Ser	Val	Ser	Ser	Asn
5				20					25					30		
	Ser	Ala	Ala	Trp	Gly	Trp	Ile	Arg	Gln	Ser	Pro	Gly	Arg	Gly	Leu	Glu
			35					40					45			
	Trp	Leu	Gly	Ile	Ile	Gln	Ile	Arg	Ser	Lys	Trp	Tyr	Asn	Asp	Tyr	Ala
		50					55					60				
	Leu	Ser	Val	Lys	Ser	Arg	Ile	Thr	Ile	Asn	Pro	Asp	Thr	Ser	Lys	Asn
10	65					70					75					80
	Gln	Phe	Ser	Leu	Gln	Leu	Asn	Ser	Val	Thr	Pro	Glu	Asp	Thr	Ala	Val
					85					90					95	
	Tyr	Tyr	Cys	Ala	Arg	Tyr	Ser	Tyr	Pro	Phe	Tyr	Ser	Ile	Asp	Tyr	Trp
				100					105					110		
15	Gly	Gln	Gly	Thr	Leu	Val	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro
			115					120					125			
	Ser	Val	Phe	Pro	Leu	Ala	Pro	Cys	Ser	Arg	Ser	Thr	Ser	Glu	Ser	Thr
			130				135					140				
	Ala	Ala	Leu	Gly	Cys	Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr
	145					150					155					160
20	Val	Ser	Trp	Asn	Ser	Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro
				165							170				175	
	Ala	Val	Leu	Gln	Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr
				180					185					190		
	Val	Pro	Ser	Ser	Ser	Leu	Gly	Thr	Lys	Thr	Tyr	Thr	Cys	Asn	Val	Asp
			195					200					205			
25	His	Lys	Pro	Ser	Asn	Thr	Lys	Val	Asp	Lys	Arg	Val	Glu	Ser	Lys	Tyr
		210					215					220				
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	225					230					235					240
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				245						250					255	
	Arg	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	Gln	Glu	Asp
				260					265					270		
	Pro	Glu	Val	Gln	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn
				275				280					285			
35	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Phe	Asn	Ser	Thr	Tyr	Arg	Val
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	Val	Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu
	305					310					315					320
	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Gly	Leu	Pro	Ser	Ser	Ile	Glu	Lys
				325						330					335	
40	Thr	Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr
				340					345					350		
	Leu	Pro	Pro	Ser	Gln	Glu	Glu	Met	Thr	Lys	Asn	Gln	Val	Ser	Leu	Thr
			355					360					365			
45																
	Cys	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu
		370					375					380				
	Ser	Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Val	Leu
	385					390					395					400
50	Asp	Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser	Arg	Leu	Thr	Val	Asp	Lys
				405						410					415	
	Ser	Arg	Trp	Gln	Glu	Gly	Asn	Val	Phe	Ser	Cys	Ser	Val	Met	His	Glu
				420					425					430		
	Ala	Leu	His	Asn	His	Tyr	Thr	Gln	Lys	Ser	Leu	Ser	Leu	Ser	Leu	Gly
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<210> 219

<211> 449

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<212> PRT

<213> Artificial Sequence

<220>

5 <223> Candidates 10EVQ, 12EVQ heavy chain with S229P, F235A/L236A

<400> 219

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				20					25					30		
	Ser	Ala	Ala	Trp	Gly	Trp	Ile	Arg	Gln	Ser	Pro	Gly	Arg	Gly	Leu	Glu
		35						40					45			
15	Trp	Leu	Gly	Ile	Ile	Gln	Lys	Arg	Ser	Lys	Trp	Tyr	Asn	Asn	Tyr	Ala
	50						55					60				
	Val	Ser	Val	Lys	Ser	Arg	Ile	Thr	Ile	Asn	Pro	Asp	Thr	Ser	Lys	Asn
	65					70					75					80
	Gln	Phe	Ser	Leu	Gln	Leu	Asn	Ser	Val	Thr	Pro	Glu	Asp	Thr	Ala	Val
					85					90					95	
20	Tyr	Tyr	Cys	Ala	Arg	Tyr	Ser	Tyr	Pro	Phe	Tyr	Ser	Ile	Asp	Tyr	Trp
				100					105					110		
	Gly	Gln	Gly	Thr	Leu	Val	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro
		115						120					125			
25	Ser	Val	Phe	Pro	Leu	Ala	Pro	Cys	Ser	Arg	Ser	Thr	Ser	Glu	Ser	Thr
		130					135					140				
	Ala	Ala	Leu	Gly	Cys	Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr
	145					150					155					160
	Val	Ser	Trp	Asn	Ser	Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro
				165					170						175	
30	Ala	Val	Leu	Gln	Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr
				180					185					190		
	Val	Pro	Ser	Ser	Ser	Leu	Gly	Thr	Lys	Thr	Tyr	Thr	Cys	Asn	Val	Asp
			195					200					205			
	His	Lys	Pro	Ser	Asn	Thr	Lys	Val	Asp	Lys	Arg	Val	Glu	Ser	Lys	Tyr
		210					215					220				
35	Gly	Pro	Pro	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Ala	Ala	Gly	Gly	Pro
	225					230					235					240
	Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser
				245						250					255	
40	Arg	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	Gln	Glu	Asp
				260					265					270		
	Pro	Glu	Val	Gln	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn
			275					280					285			
	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Phe	Asn	Ser	Thr	Tyr	Arg	Val
		290					295					300				
45	Val	Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu

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	305				310				315					320		
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					325					330					335	
5	Thr	Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr
				340					345					350		
	Leu	Pro	Pro	Ser	Gln	Glu	Glu	Met	Thr	Lys	Asn	Gln	Val	Ser	Leu	Thr
				355				360					365			
	Cys	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu
		370					375				380					
10	Ser	Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Val	Leu
	385					390					395				400	
	Asp	Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser	Arg	Leu	Thr	Val	Asp	Lys
				405						410				415		
	Ser	Arg	Trp	Gln	Glu	Gly	Asn	Val	Phe	Ser	Cys	Ser	Val	Met	His	Glu
15				420					425				430			
	Ala	Leu	His	Asn	His	Tyr	Thr	Gln	Lys	Ser	Leu	Ser	Leu	Ser	Leu	Gly
			435					440					445			
	Lys															

20 <210> 220
 <211> 448
 <212> PRT
 <213> Artificial Sequence

25 <220>
 <223> EVQ variant mAb14 and mAb15 full length heavy Chain S229P, F235A/L236A
 <400> 220

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	Ser	Leu	Lys	Ile	Ser	Cys	Lys	Gly	Ser	Gly	Tyr	Ser	Phe	Thr	Asn	Tyr
				20					25					30		
5	Trp	Val	Gly	Trp	Val	Arg	Gln	Met	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Met
			35					40					45			
	Gly	Phe	Ile	Asp	Pro	Ser	Asp	Ser	Tyr	Thr	Asn	Tyr	Ala	Pro	Ser	Phe
		50					55					60				
	Gln	Gly	Gln	Val	Thr	Ile	Ser	Ala	Asp	Lys	Ser	Ile	Ser	Thr	Ala	Tyr
10	65					70					75					80
	Leu	Gln	Trp	Ser	Ser	Leu	Lys	Ala	Ser	Asp	Thr	Ala	Met	Tyr	Tyr	Cys
					85					90					95	
	Ala	Arg	Glu	Leu	Tyr	Gln	Gly	Tyr	Met	Asp	Thr	Phe	Asp	Ser	Trp	Gly
				100					105					110		
15	Gln	Gly	Thr	Leu	Val	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro	Ser
			115						120					125		
	Val	Phe	Pro	Leu	Ala	Pro	Cys	Ser	Arg	Ser	Thr	Ser	Glu	Ser	Thr	Ala
		130					135					140				
	Ala	Leu	Gly	Cys	Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val
	145					150					155					160
20	Ser	Trp	Asn	Ser	Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro	Ala
					165					170					175	
	Val	Leu	Gln	Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val
				180					185					190		
	Pro	Ser	Ser	Ser	Leu	Gly	Thr	Lys	Thr	Tyr	Thr	Cys	Asn	Val	Asp	His
25			195					200					205			
	Lys	Pro	Ser	Asn	Thr	Lys	Val	Asp	Lys	Arg	Val	Glu	Ser	Lys	Tyr	Gly
		210					215					220				
	Pro	Pro	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Ala	Ala	Gly	Gly	Pro	Ser
	225					230					235					240
30	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser	Arg
					245				250					255		
	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	Gln	Glu	Asp	Pro
				260					265					270		
35	Glu	Val	Gln	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn	Ala
			275					280					285			
	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Phe	Asn	Ser	Thr	Tyr	Arg	Val	Val
		290					295					300				
40	Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu	Tyr
	305					310					315					320
	Lys	Cys	Lys	Val	Ser	Asn	Lys	Gly	Leu	Pro	Ser	Ser	Ile	Glu	Lys	Thr
					325					330					335	
	Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr	Leu
				340					345					350		
45	Pro	Pro	Ser	Gln	Glu	Glu	Met	Thr	Lys	Asn	Gln	Val	Ser	Leu	Thr	Cys
			355					360					365			
	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu	Ser
		370					375					380				
	Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Val	Leu	Asp
	385					390					395					400
50	Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser	Arg	Leu	Thr	Val	Asp	Lys	Ser
					405					410					415	
	Arg	Trp	Gln	Glu	Gly	Asn	Val	Phe	Ser	Cys	Ser	Val	Met	His	Glu	Ala
				420					425					430		
	Leu	His	Asn	His	Tyr	Thr	Gln	Lys	Ser	Leu	Ser	Leu	Ser	Leu	Gly	Lys
55			435					440					445			

Claims

1. An isolated antibody or fragment thereof reactive with toll-like receptor 3 (TLR3), comprising both a heavy chain and a light chain variable region and wherein the antibody comprises:
 - a. the heavy chain CDR 1, 2 and 3 amino acid sequences as shown in SEQ ID NO:s 82, 86 and 84; and
 - b. the light chain CDR 1, 2 and 3 amino acid sequences as shown in SEQ ID NO:s 79, 80 and 87.
2. The isolated antibody or fragment of claim 1, comprising the heavy chain variable region of SEQ ID NO: 216 and the light chain variable region of SEQ ID NO: 41.
3. The isolated antibody or fragment of claim 1 or claim 2, comprising the heavy chain of SEQ ID NO: 220 and the light chain of SEQ ID NO: 156.
4. The isolated antibody or fragment of any one of claims 1-3, wherein the antibody has at least one of the following properties:
 - a. reduces human TLR3 biological activity in an *in vitro* poly(I:C) NF- κ B reporter gene assay >50% at <1 μ g/ml;
 - b. inhibits >60% of IL-6 or CXCL10/IP-10 production from BEAS-2B cells stimulated with <100 ng/ml poly(I:C) at <10 μ g/ml;
 - c. inhibits >50% of IL-6 or CXCL10/IP-10 production from BEAS-2B cells stimulated with <100 ng/ml poly(I:C) at <0.4 μ g/ml;
 - d. inhibits >50% of IL-6 production from NHBE cells stimulated with 62.5 ng/ml poly(I:C) at <5 μ g/ml;
 - e. inhibits >50% of IL-6 production from NHBE cells stimulated with 62.5 ng/ml poly(I:C) at <1 μ g/ml;
 - f. inhibits >20% of poly(I:C)-induced IFN- γ , IL-6 or IL-12 production by PBMC at <1 μ g/ml;
 - g. inhibits cynomolgus TLR3 biological activity in an *in vitro* NF- κ B reporter gene assay with IC₅₀ <10 μ g/ml; or
 - h. inhibits cynomolgus TLR3 biological activity in an *in vitro* ISRE reporter gene assay with IC₅₀ <5 μ g/ml.
5. The isolated antibody or fragment of any one of the preceding
 - a. the antibody is fully human;
 - b. the antibody or fragment is human-adapted;
 - c. the antibody is conjugated to polyethylene glycol; or
 - d. the Fc domain comprises S229P, P235A or L236A mutations.
6. The isolated antibody or fragment of any one of the preceding claims having an IgG4 isotype.
7. A pharmaceutical composition comprising the isolated antibody or fragment of any one of the preceding claims and a pharmaceutically acceptable carrier.
8. The isolated antibody or fragment of any one of claims 1-6 or the pharmaceutical composition of claim 7 for use in therapy.
9. The isolated antibody or fragment of any one of claims 1-6 or the pharmaceutical composition of claim 7 for use in a method of treating:
 - a) an inflammatory condition, optionally wherein the inflammatory condition:
 - i) affects a tissue selected from a group consisting of the respiratory tract, lung, the gastrointestinal tract, small intestine, large intestine, colon, rectum, the cardiovascular system, cardiac tissue, blood vessels, joint, bone and synovial tissue, cartilage, epithelium, endothelium, hepatic or adipose tissue;
 - ii) is associated with increased TLR3-mediated neutrophil infiltration into the tissue;
 - iii) is an inflammatory pulmonary condition, optionally:
 - I) asthma or chronic obstructive pulmonary disease (COPD);
 - II) induced by Nontypeable Haemophilus influenza; or
 - III) airway hyperresponsiveness, optionally associated with asthma, allergic rhinitis, COPD, or cystic fibrosis;

- iv) is an inflammatory bowel disease;
- v) is associated with gastrointestinal ulceration, optionally infectious colitis, ischemic colitis, collagenous or lymphocytic colitis or necrotizing enterocolitis; or
- vi) is an autoimmune disease, optionally rheumatoid

- b) type II diabetes;
- c) hyperglycemia; or
- d) hyperinsulinemia;

wherein the method comprises administering a therapeutically effective amount of the isolated antibody or fragment or the pharmaceutical composition to a patient in need thereof for a time sufficient to treat or prevent the inflammatory condition, the type II diabetes, hyperglycemia or insulin resistance.

- 10.** The isolated antibody or fragment of any one of claims 1-6 or the pharmaceutical composition of claim 7 for use in a method of treating or preventing:

- a) a systemic inflammatory condition, optionally cytokine storm or hypercytokinemia, systemic inflammatory response syndrome (SIRS), graft versus host disease (GVHD), acute respiratory distress syndrome (ARDS), severe acute respiratory distress syndrome (SARS), catastrophic anti-phospholipid syndrome, severe viral infections, influenza, pneumonia, shock, or sepsis; or
- b) viral infections, optionally influenza A virus infection;

wherein the method comprises administering a therapeutically effective amount of the isolated antibody or fragment or the pharmaceutical composition to a patient in need thereof for a time sufficient to treat or prevent the systemic inflammatory condition or viral infection.

Patentansprüche

- 1.** Isolierter Antikörper oder Fragment davon, reaktiv mit TLR3 (Toll-like Receptor 3), umfassend sowohl eine Schwere-Kette- als auch eine Leichte-Kette-variable-Region, und wobei der Antikörper Folgendes umfasst:

- a. die Schwere-Kette-CDR-1-, -2- und -3-Amino-säuresequenzen gemäß SEQ ID NO: 82, 86 und 84; und
- b. die Leichte-Kette-CDR-1-, -2- und -3-Amino-säuresequenzen gemäß SEQ ID NO: 79, 80 und 87.

- 2.** Isolierter Antikörper oder Fragment nach Anspruch 1, umfassend die Schwere-Kette-variable-Region unter SEQ ID NO: 216 und die Leichte-Kette-variable-Region unter SEQ ID NO: 41.

- 3.** Isolierter Antikörper oder Fragment nach Anspruch 1 oder Anspruch 2, umfassend die schwere Kette unter SEQ ID NO: 220 und die leichte Kette unter SEQ ID NO: 156.

- 4.** Isolierter Antikörper oder Fragment nach einem der Ansprüche 1-3, wobei der Antikörper wenigstens eine der folgenden Eigenschaften aufweist:

- a. reduziert menschliche biologische TLR3-Aktivität in einem In-vitro-Poly(I:C)-NF-κB-Reporter-Gen-Test >50% bei <1 µg/ml;
- b. hemmt >60% der IL-6- oder CXCL10/IP-10-Produktion von mit <100 ng/ml Poly(I:C) stimulierten BEAS-2B-Zellen bei <10 µg/ml;
- c. hemmt >50% der IL-6- oder CXCL10/IP-10-Produktion von mit <100 ng/ml Poly(I:C) stimulierten BEAS-2B-Zellen bei <0,4 µg/ml;
- d. hemmt >50% der IL-6-Produktion von mit 62,5 ng/ml Poly(I:C) stimulierten NHBE-Zellen bei <5 µg/ml;
- e. hemmt >50% der IL-6-Produktion von mit 62,5 ng/ml Poly(I:C) stimulierten NHBE-Zellen bei <1 µg/ml;
- f. hemmt >20% der durch Poly(I:C) induzierten IFN-γ-, IL-6- oder IL-12-Produktion durch PBMC bei <1 µg/ml;
- g. hemmt biologische Javaneraffe-TLR3-Aktivität in einem In-vitro-NF-κB-Reporter-Gen-Test mit IC₅₀ <10 µg/ml; oder
- h. hemmt biologische Javaneraffe-TLR3-Aktivität in einem In-vitro-ISRE-Reporter-Gen-Test mit IC₅₀ <5 µg/ml.

- 5.** Isolierter Antikörper oder Fragment nach einem der vorhergehenden Ansprüche, wobei:

- a. der Antikörper vollständig menschlich ist;
- b. der Antikörper bzw. das Fragment an den Menschen angepasst ist;
- c. der Antikörper an Polyethylenglykol konjugiert ist; oder
- d. die Fc-Domäne S229P-, P235A- oder L236A-Mutationen umfasst.

- 5
6. Isolierter Antikörper oder Fragment nach einem der vorhergehenden Ansprüche mit einem IgG4-Isotyp.
7. Pharmazeutische Zusammensetzung, umfassend den isolierten Antikörper bzw. das Fragment nach einem der vorhergehenden Ansprüche und einen pharmazeutisch unbedenklichen Träger.
- 10
8. Isolierter Antikörper oder Fragment nach einem der Ansprüche 1-6 oder pharmazeutische Zusammensetzung nach Anspruch 7 zur Verwendung in der Therapie.
9. Isolierter Antikörper oder Fragment nach einem der Ansprüche 1-6 oder pharmazeutische Zusammensetzung nach
- 15 Anspruch 7 zur Verwendung bei einem Verfahren zur Behandlung:

a) eines Entzündungsleidens, gegebenenfalls wobei das Entzündungsleiden:

- 20
- i) ein Gewebe betrifft, das aus einer aus den Atemwegen, der Lunge, dem Magen-DarmTrakt, Dünndarm, Dickdarm, Kolon, Rektum, dem Herz-Kreislauf-System, Herzgewebe, Blutgefäßen, Gelenk-, Knochen- und Synovialgewebe, Knorpel, Epithel, Endothel, Leber- oder Fettgewebe bestehenden Gruppe ausgewählt ist;
 - ii) mit erhöhter TLR3-vermittelter Neutrophileninfiltration in das Gewebe assoziiert ist;
 - iii) ein entzündliches Lungenleiden ist, gegebenenfalls:

- 25
- I) Asthma oder chronisch obstruktive Lungenerkrankung (Chronic Obstructive Pulmonary Disease, COPD);
 - II) induziert durch Nontypeable Haemophilus influenza; oder
 - III) Atemwegs-Hyperreaktivität, gegebenenfalls assoziiert mit Asthma, allergischer Rhinitis, COPD oder Mukoviszidose;
- 30

- iv) eine entzündliche Darmkrankheit ist;
 - v) mit Magen-Darm-Geschwüren, gegebenenfalls infektiöser Colitis, ischämischer Colitis, kollagener oder lymphozytischer Colitis oder nekrotisierender Enterocolitis assoziiert ist; oder
 - vi) eine Autoimmunkrankheit ist, gegebenenfalls rheumatoide Arthritis;
- 35

- b) von Typ-II-Diabetes;
- c) von Hyperglykämie; oder
- d) von Hyperinsulinämie;

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wobei das Verfahren Verabreichen einer therapeutisch wirksamen Menge des isolierten Antikörpers oder Fragments oder der pharmazeutischen Zusammensetzung an einen dies benötigenden Patienten über einen zum Behandeln oder Vorbeugen des Entzündungsleidens, des Typ-II-Diabetes, der Hyperglykämie oder Insulinresistenz ausreichenden Zeitraum umfasst.

- 45
10. Isolierter Antikörper oder Fragment nach einem der Ansprüche 1-6 oder pharmazeutische Zusammensetzung nach Anspruch 7 zur Verwendung bei einem Verfahren zur Behandlung oder Vorbeugung:

- 50
- a) eines systemischen Entzündungsleidens, gegebenenfalls von Cytokin-Sturm bzw. Hypercytokinämie, SIRS (Systemic Inflammatory Response Syndrome), Graft-versus-Host-Reaktion (Graftversus Host Disease, GVHD), ARDS (Acute Respiratory Distress Syndrome), schwerem akutem Atemwegssyndrom (Severe Acute Respiratory Syndrome, SARS), katastrophalem Antiphospholipidsyndrom, schweren Virusinfektionen, Influenza, Lungenentzündung, Schock oder Sepsis; oder
 - b) von Virusinfektionen, gegebenenfalls Influenza-A-Virus-Infektion;

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wobei das Verfahren Verabreichen einer therapeutisch wirksamen Menge des isolierten Antikörpers oder Fragments oder der pharmazeutischen Zusammensetzung an einen dies benötigenden Patienten über einen zum Behandeln oder Vorbeugen des systemischen Entzündungsleidens bzw. der Virusinfektion ausreichenden Zeitraum umfasst.

Revendications

1. Anticorps isolé ou fragment de celui-ci réactif avec le récepteur toll-like 3 (TLR3), comprenant à la fois une région variable de chaîne lourde et de chaîne légère et l'anticorps comprenant :

- a. les séquences d'acides aminés CDR 1, 2 et 3 de chaîne lourde comme décrit dans SEQ ID NO: 82, 86 et 84 ; et
- b. les séquences d'acides aminés CDR 1, 2 et 3 de chaîne légère comme décrit dans SEQ ID NO: 79, 80 et 87.

2. Anticorps isolé ou fragment de la revendication 1, comprenant la région variable de chaîne lourde de SEQ ID NO: 216 et la régions variables de chaîne légère de SEQ ID NO: 41.

3. Anticorps isolé ou fragment de la revendication 1 ou la revendication 2, comprenant la chaîne lourde de SEQ ID NO: 220 et la chaîne légère de SEQ ID NO: 156.

4. Anticorps isolé ou fragment de l'une quelconque des revendications 1 à 3, l'anticorps ayant au moins une des propriétés suivantes :

- a. réduit l'activité biologique de TLR3 humain dans un essai de gène rapporteur poly(I:C) NF- κ B *in vitro* > 50 % à < 1 μ g/ml ;
- b. inhibe > 60 % de la production de IL-6 ou CXCL10/IP-10 de cellules BEAS-2B stimulées avec < 100 ng/ml de poly(I:C) à < 10 μ g/ml ;
- c. inhibe > 50 % de la production de IL-6 ou CXCL10/IP-10 de cellules BEAS-2B stimulées avec < 100 ng/ml de poly(I:C) à < 0,4 μ g/ml ;
- d. inhibe > 50 % de la production de IL-6 de cellules NHBE stimulées avec 62,5 ng/ml de poly(I:C) à < 5 μ g/ml ;
- e. inhibe > 50 % de la production de IL-6 de cellules NHBE stimulées avec 62,5 ng/ml de poly(I:C) à < 1 μ g/ml ;
- f. inhibe > 20 % de la production de IFN- γ , IL-6 ou IL-12 induite par poly(I:C) par des PBMC à < 1 μ g/ml ;
- g. inhibe l'activité biologique TLR3 de cynomolgus dans un essai de gène rapporteur NF- κ B *in vitro* avec CI50 < 10 μ g/ml ; ou
- h. inhibe l'activité biologique TLR3 de cynomolgus dans un essai de gène rapporteur ISRE *in vitro* avec CI50 < 5 μ g/ml.

5. Anticorps isolé ou fragment de l'une quelconque des revendications précédentes, où :

- a. l'anticorps est totalement humain ;
- b. l'anticorps ou fragment est adapté aux humains ;
- c. l'anticorps est conjugué au polyéthylène glycol ; ou
- d. le domaine Fc comprend les mutations S229P, P235A ou L236A.

6. Anticorps isolé ou fragment de l'une quelconque des revendications précédentes ayant un isotype IgG4.

7. Composition pharmaceutique comprenant l'anticorps isolé ou fragment de l'une quelconque des revendications précédentes et un véhicule pharmaceutiquement acceptable.

8. Anticorps isolé ou fragment de l'une quelconque des revendications 1 à 6 ou composition pharmaceutique de la revendication 7 pour utilisation en thérapie.

9. Anticorps isolé ou fragment de l'une quelconque des revendications 1 à 6 ou composition pharmaceutique de la revendication 7 pour utilisation dans un procédé de traitement :

- a) une affection inflammatoire, facultativement où l'affection inflammatoire :

- i) affecte un tissu choisi dans un groupe constitué de tissu des voies respiratoires, des poumons, du tube digestif, de l'intestin grêle, du gros intestin, du côlon, du rectum, du système cardiovasculaire, cardiaque, vasculaire, articulaire, osseux et synovial tissu, du cartilage, de l'épithélium, de l'endothélium, de tissu hépatique ou adipeux ;
- ii) est associée à une infiltration de neutrophiles médiée par TLR3 augmentée dans le tissu ;
- iii) est une affection inflammatoire pulmonaire, facultativement :

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- I) l'asthme ou la bronchopneumopathie chronique obstructive (BPCO) ;
- II) induite par *Haemophilus influenza* non typable ; ou
- III) une hyperréactivité des voies respiratoires, facultativement associée à l'asthme, la rhinite allergique, BPCO ou la mucoviscidose ;

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- iv) est un syndrome abdominal inflammatoire ;
- v) est associée à une ulcération gastro-intestinale, éventuellement une colite infectieuse, une colite ischémique, une colite collagénique ou lymphocytaire ou une entérocolite nécrosante ; ou
- vi) est une maladie auto-immune, facultativement la polyarthrite rhumatoïde ;

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- b) le diabète de type II ;
- c) l'hyperglycémie ; ou
- d) l'hyperinsulinémie ;

15

le procédé comprenant l'administration d'une quantité thérapeutiquement efficace de l'anticorps isolé ou fragment ou de la composition pharmaceutique à un patient en ayant besoin pendant un temps suffisant pour traiter ou prévenir l'affection inflammatoire, le diabète de type II, l'hyperglycémie ou l'insulinorésistance.

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- 10.** Anticorps isolé ou fragment de l'une quelconque des revendications 1 à 6 ou composition pharmaceutique de la revendication 7 pour utilisation dans un procédé de traitement ou de prévention de :

25

- a) une affection inflammatoire systémique, éventuellement une cascade de cytokines ou une hypercytokinémie, un syndrome de réponse inflammatoire systémique (SRIS), la maladie du greffon contre l'hôte (GVHD), le syndrome de détresse respiratoire aigu (SDRA), le syndrome de détresse respiratoire aigu sévère (SRSA), Le syndrome catastrophique des antiphospholipides, les infections virales sévères, la grippe, la pneumonie, un choc ou un sepsis ; ou
- b) des infections virales, éventuellement une infection par le virus de la grippe A ;

30

le procédé comprenant l'administration d'une quantité thérapeutiquement quantité efficace de l'anticorps isolé ou fragment ou de la composition pharmaceutique à un patient en ayant besoin pendant un temps suffisant pour traiter ou prévenir l'affection inflammatoire systémique ou l'infection virale.

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Figure 1

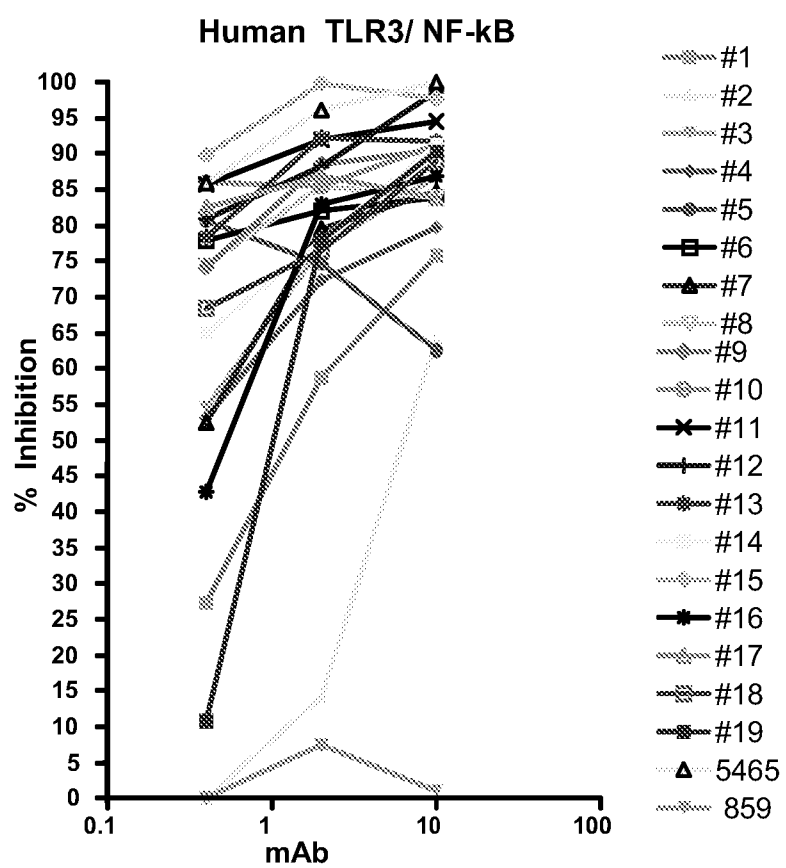


Figure 2

Figure 2A

mAb [ug/ml]		IL6	IP-10	RANTES	MCP-1	IL8
#1	10	36	66	11	23	34
	2	30	65	28	19	35
	0.4	10	34	9	14	20
#2	10	35	52	13	11	35
	2	41	76	22	26	33
	0.4	21	57	19	13	13
#3	10	47	65	23	37	44
	2	49	82	26	35	50
	0.4	26	25	8	19	32
#4	10	98	100	100	83	87
	2	46	81	31	29	50
	0.4	42	54	17	28	45
#5	10	69	87	47	55	63
	2	60	82	33	42	55
	0.4	41	61	7	26	46
#6	10	70	89	49	56	66
	2	57	81	29	38	58
	0.4	58	80	29	35	56
#7	10	71	91	50	60	67
	2	67	85	42	50	63
	0.4	49	72	27	44	50
#8	10	61	78	29	41	41
	2	39	37	3	32	34
	0.4	46	67	14	31	46
#9	10	59	83	37	52	45
	2	55	83	33	41	53
	0.4	48	66	20	40	46
#10	10	75	91	60	60	65
	2	62	82	37	48	58
	0.4	53	73	30	48	51

Figure 2B

mAb [ug/ml]	IL6	IP-10	RANTES	MCP-1	IL8
#11 10	83	96	74	71	55
2	62	83	32	55	60
0.4	61	77	29	46	54
#12 10	74	91	52	57	27
2	69	88	39	53	53
0.4	55	79	28	43	51
#13 10	87	97	81	72	80
2	71	88	50	51	68
0.4	66	80	24	49	60
#14 10	84	90	59	70	80
2	72	85	40	57	66
0.4	61	80	35	46	57
#15 10	84	93	65	70	79
2	69	84	31	55	69
0.4	59	66	18	55	56
#16 10	75	84	42	54	65
2	-12	4	-20	-20	5
0.4	3	-17	-3	-17	6
#17 10	49	82	34	18	47
2	46	79	27	11	43
0.4	26	63	15	-1	34
#18 10	37	76	22	11	31
2	34	62	24	9	21
0.4	31	33	15	11	26
#19 10	32	41	11	9	39
2	32	59	12	14	36
0.4	33	47	5	-3	21
5465 10	78	94	63	48	68
2	56	79	36	29	55
0.4	57	77	25	33	47
859 10	16	57	3	10	17
2	29	55	10	10	10
0.4	1	36	-4	2	-3

Figure 3

Figure 3A

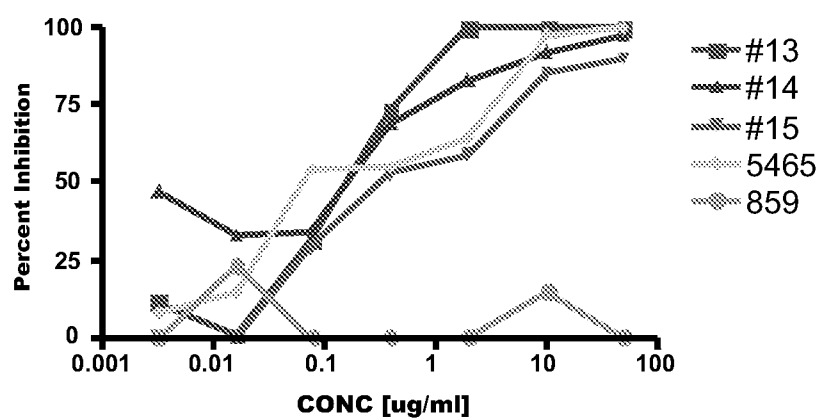


Figure 3B

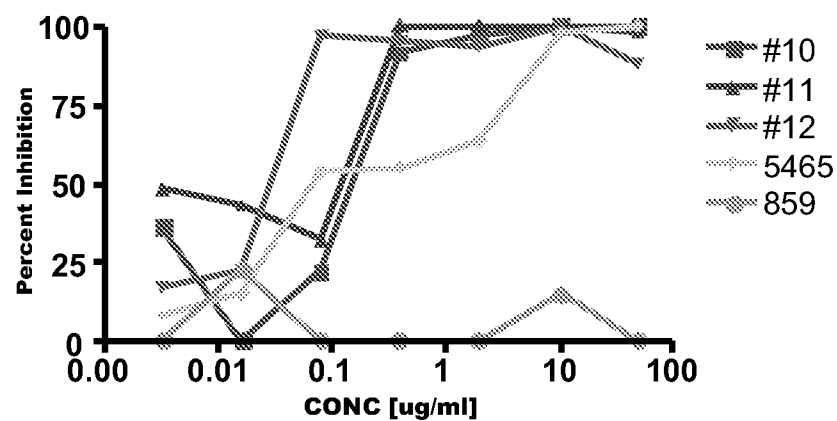


Figure 4

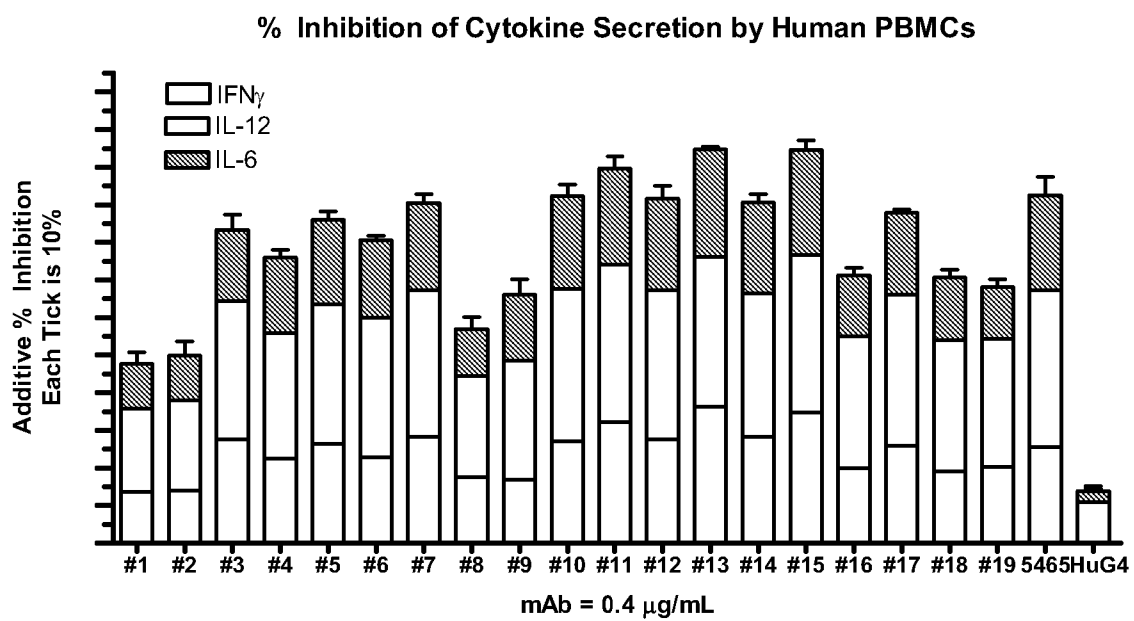


Figure 5

Figure 5A

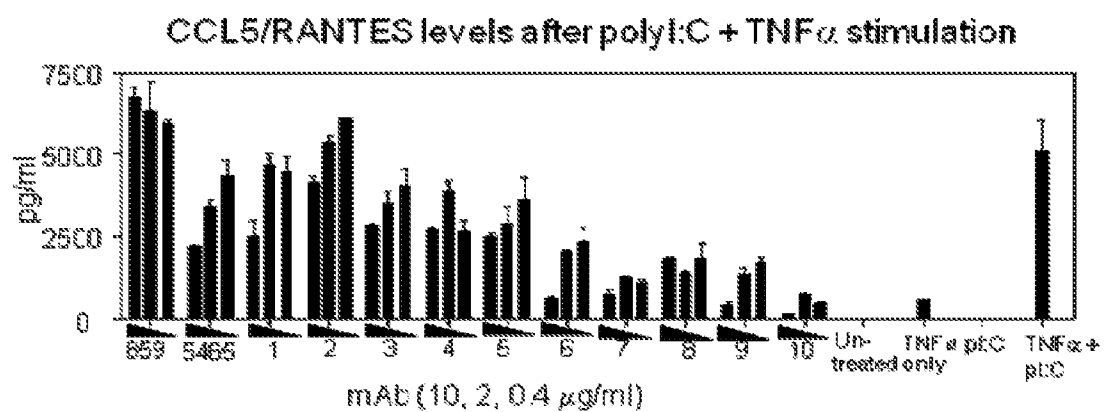


Figure 5B

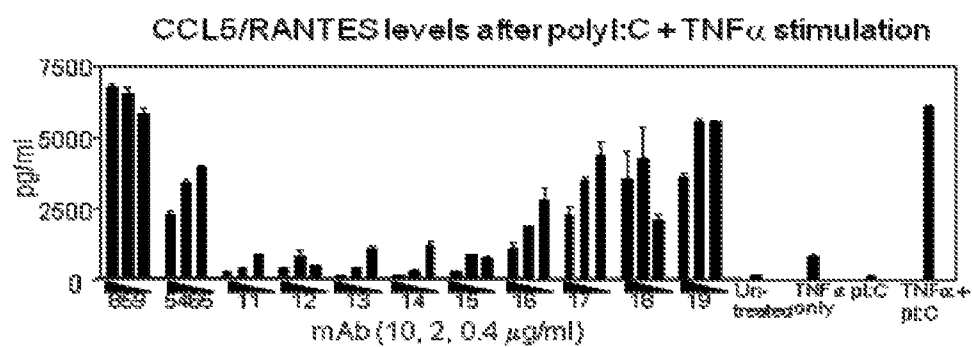


Figure 6

Figure 6A

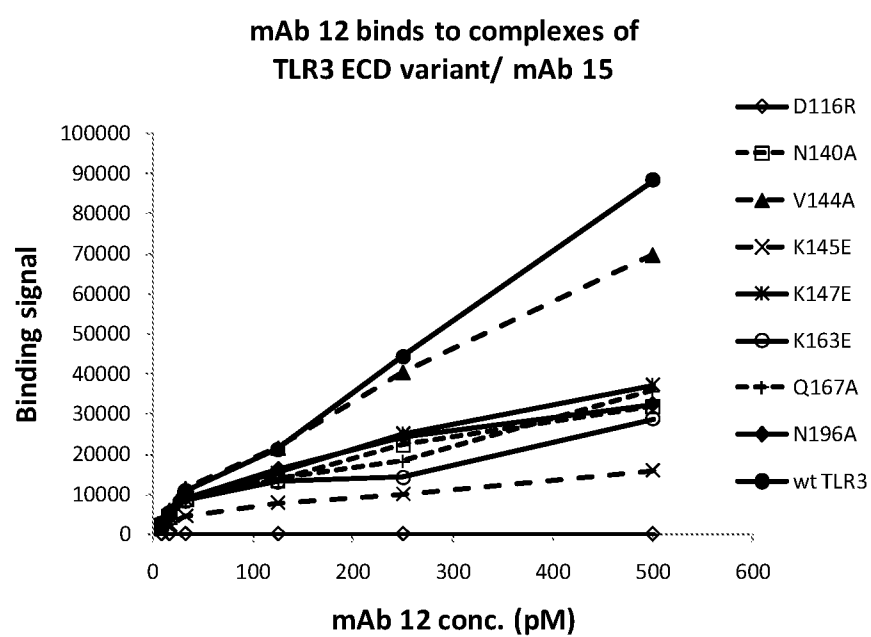


Figure 6B

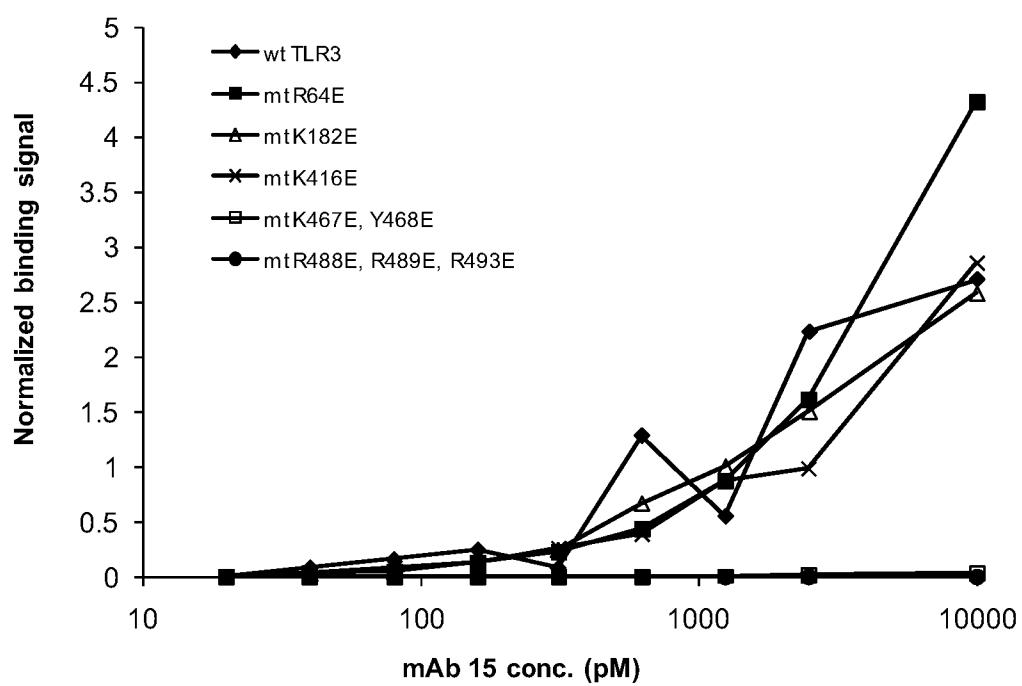


Figure 6C

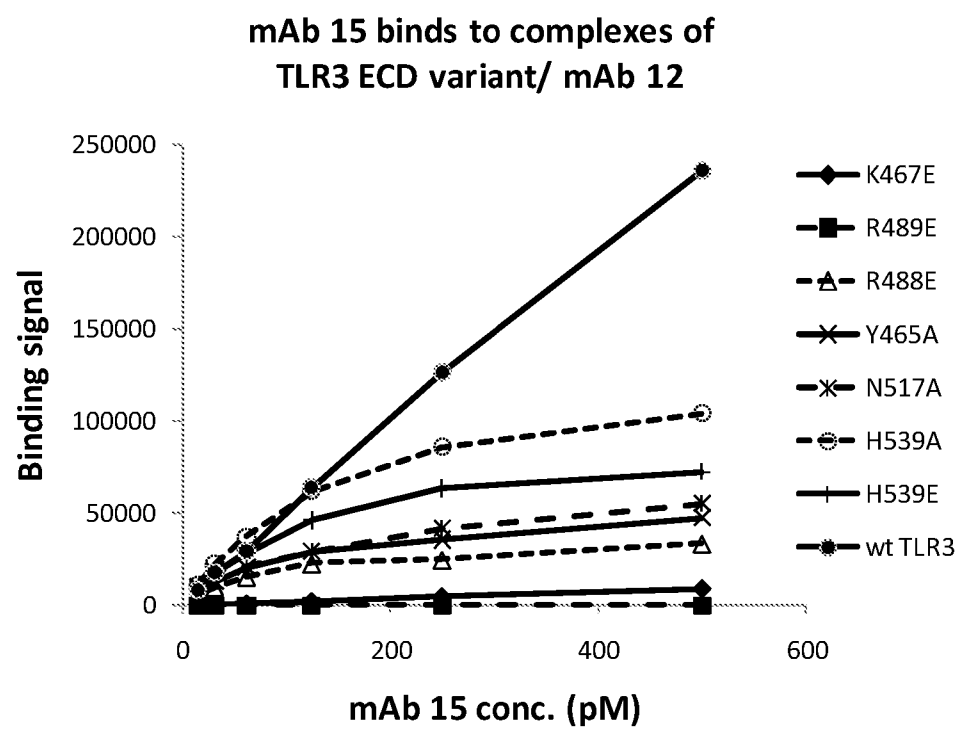


Figure 7

Figure 7A

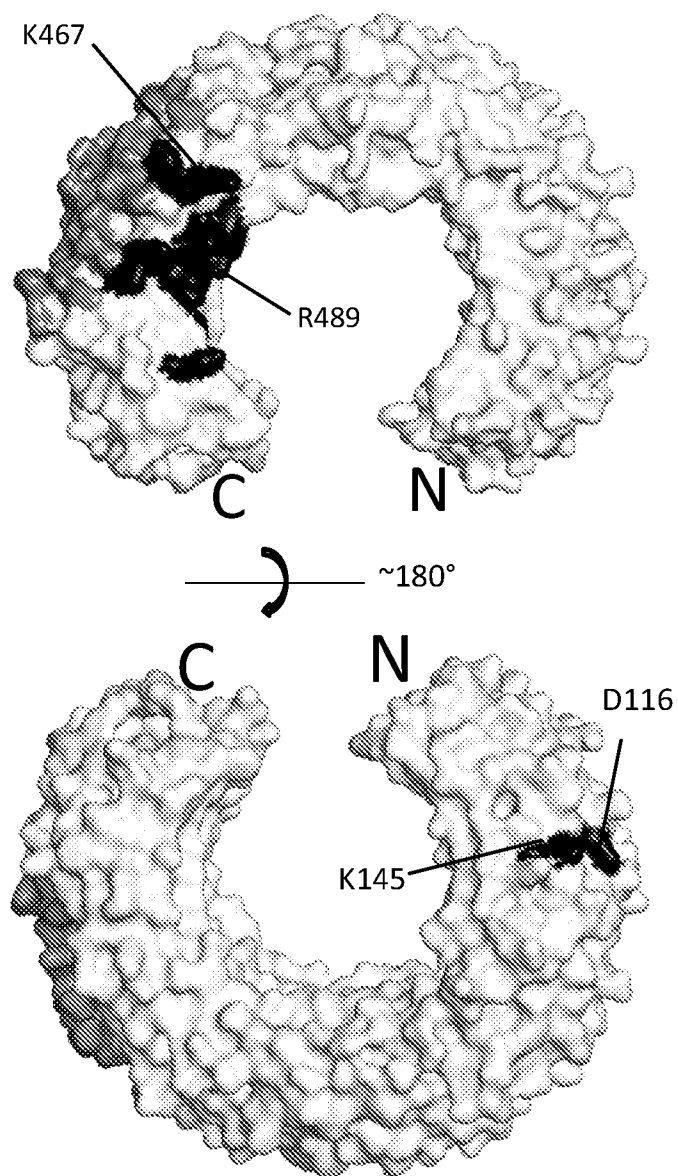


Figure 7B

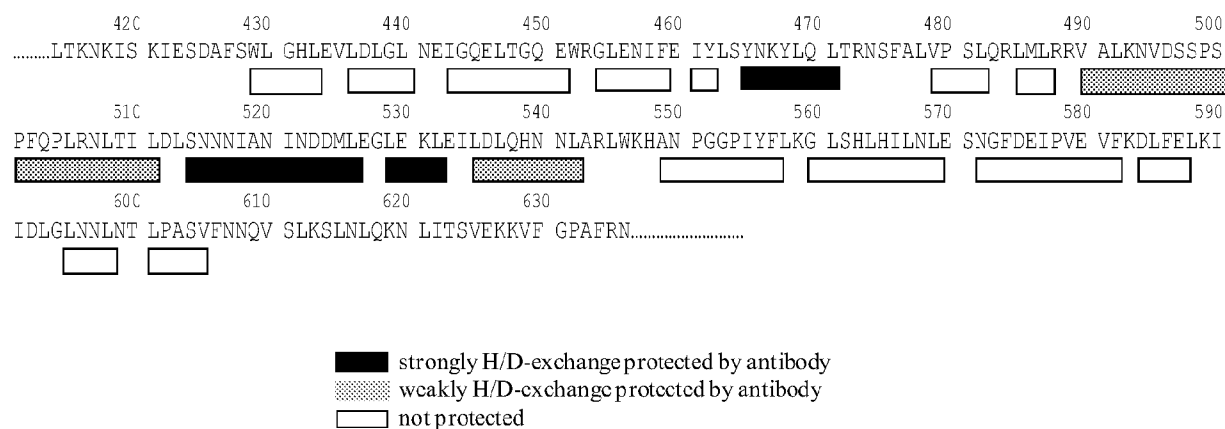
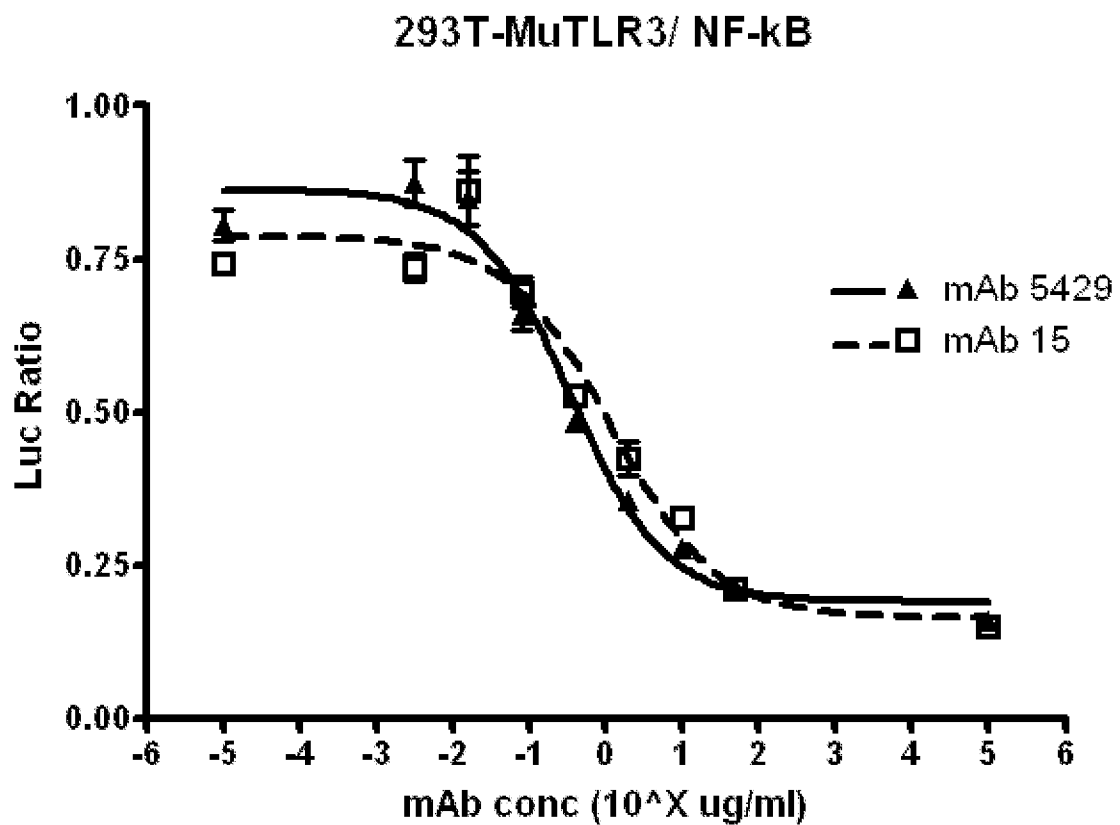


Figure 8

Figure 8A



IC50 (ug/ml)	5429	mAb 15
	0.3437	1.176

Figure 8B

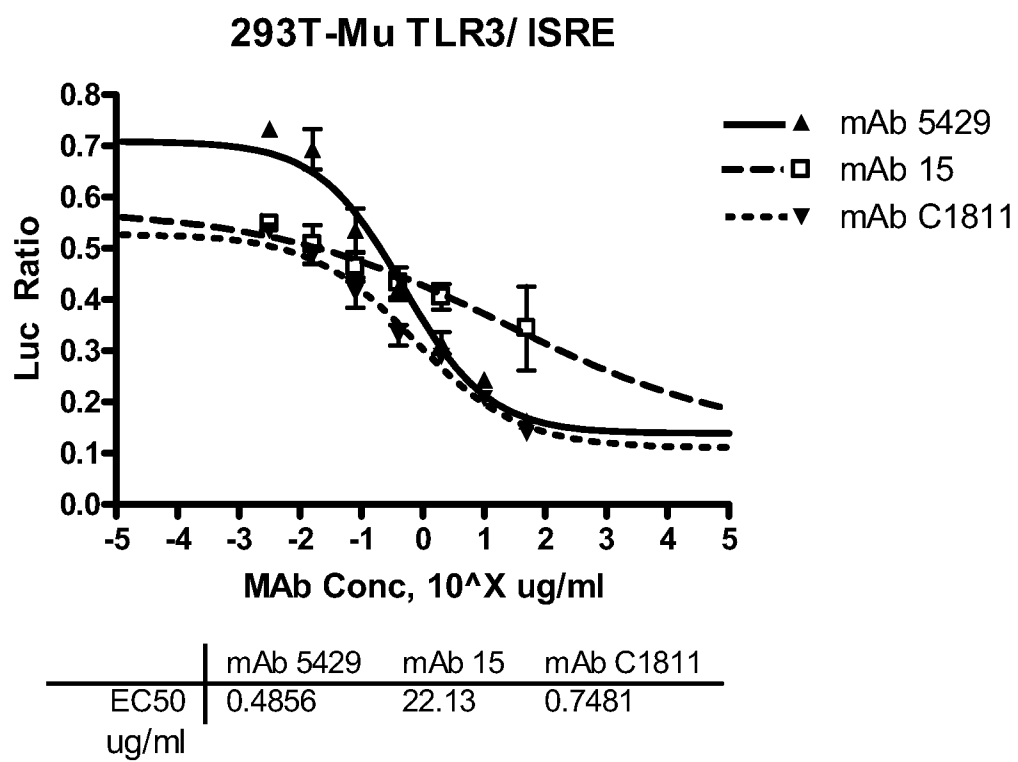


Figure 9

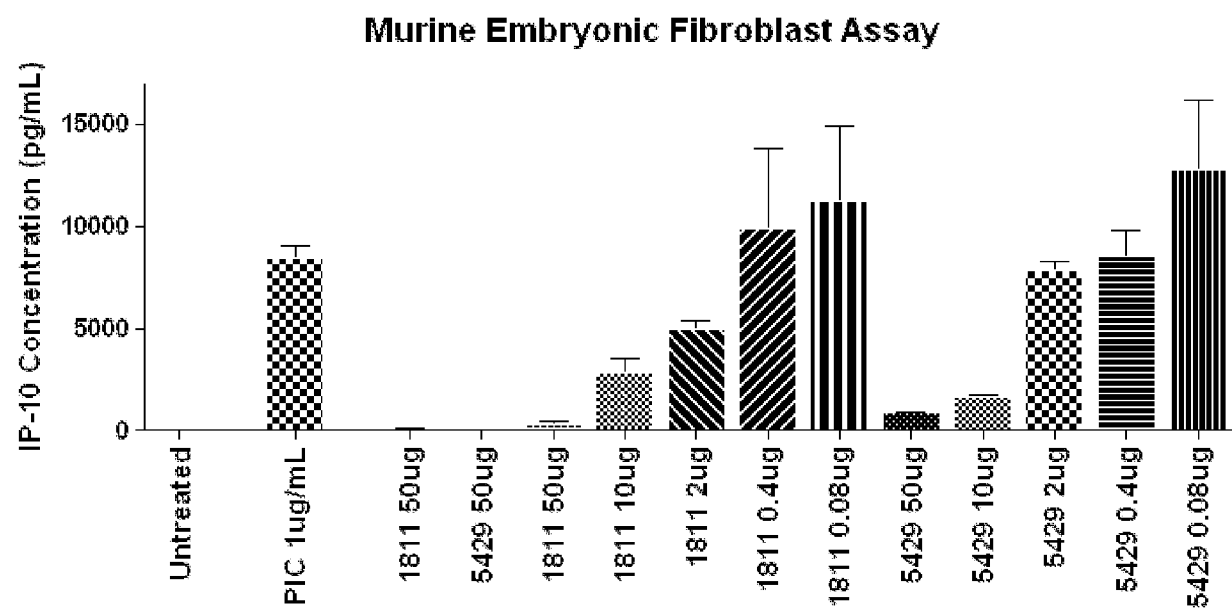


Figure 10

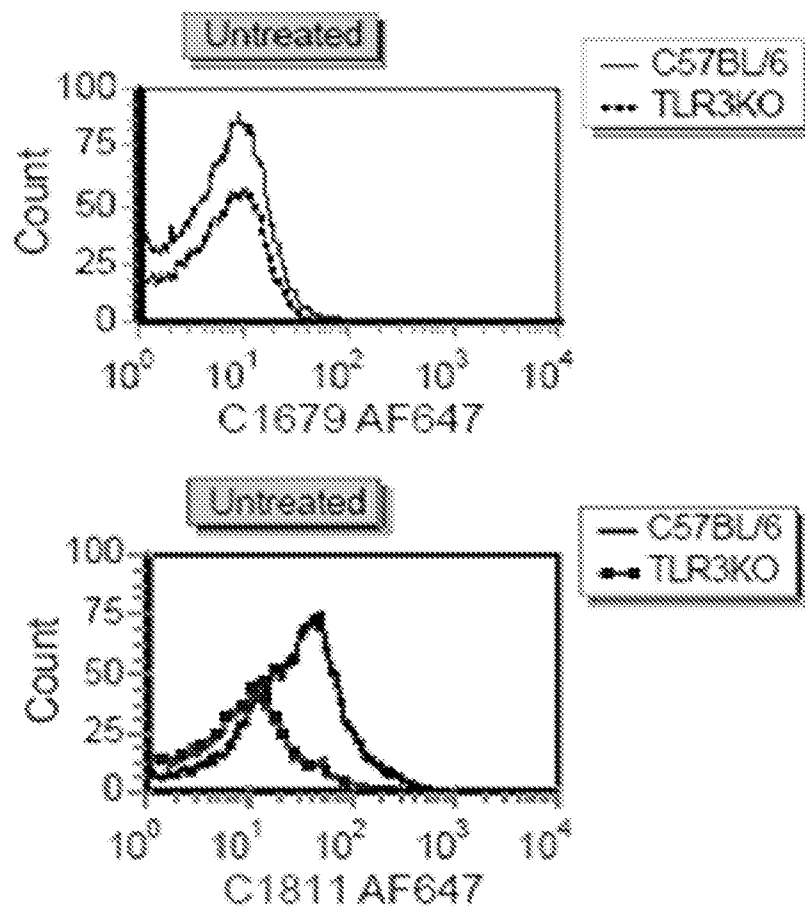


Figure 11

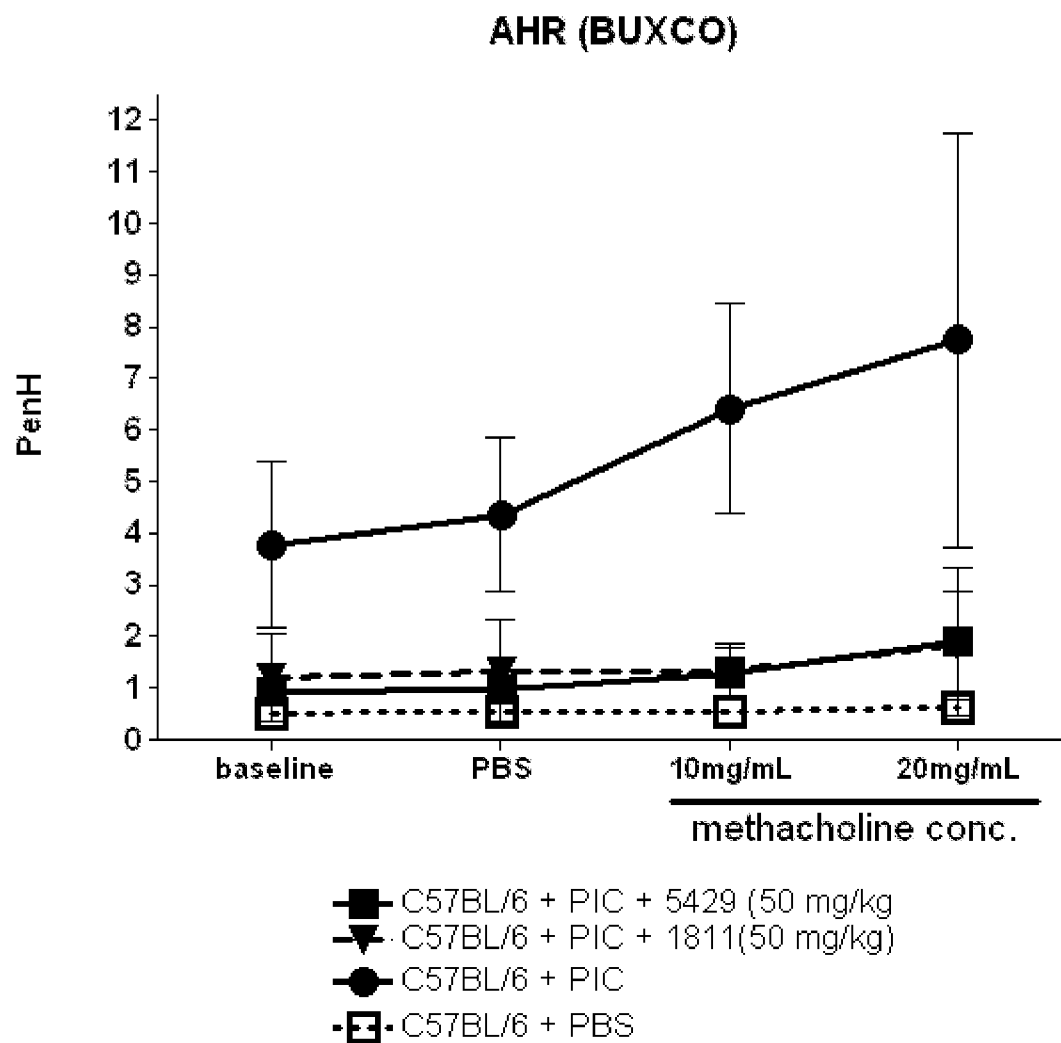


Figure 12

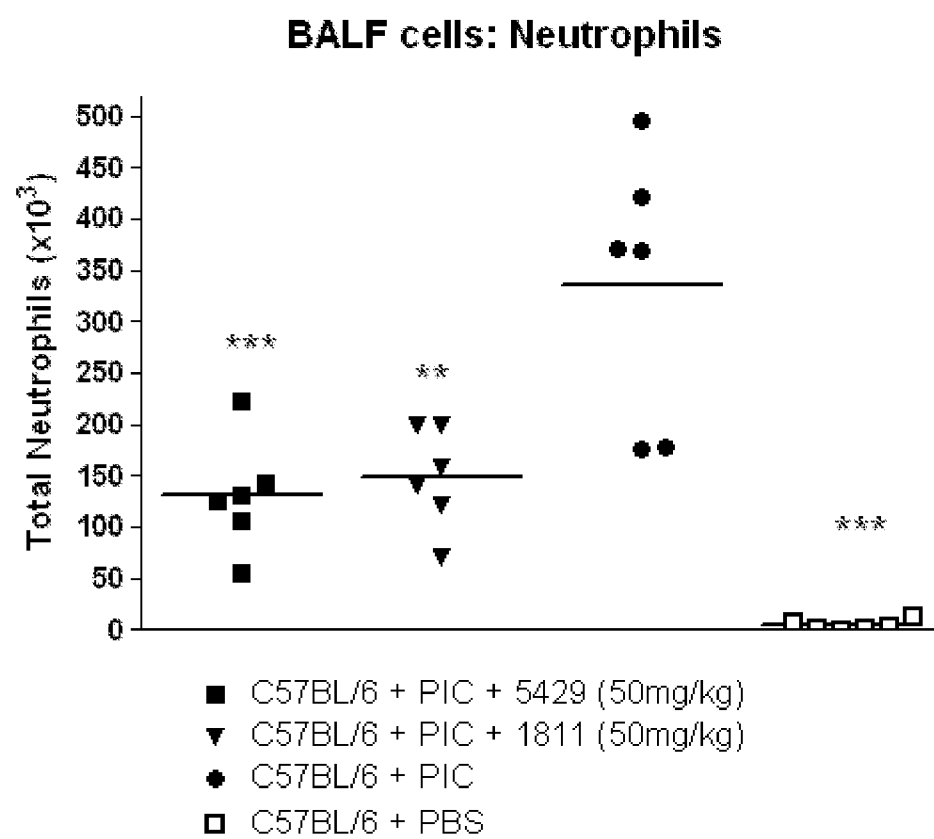


Figure 13

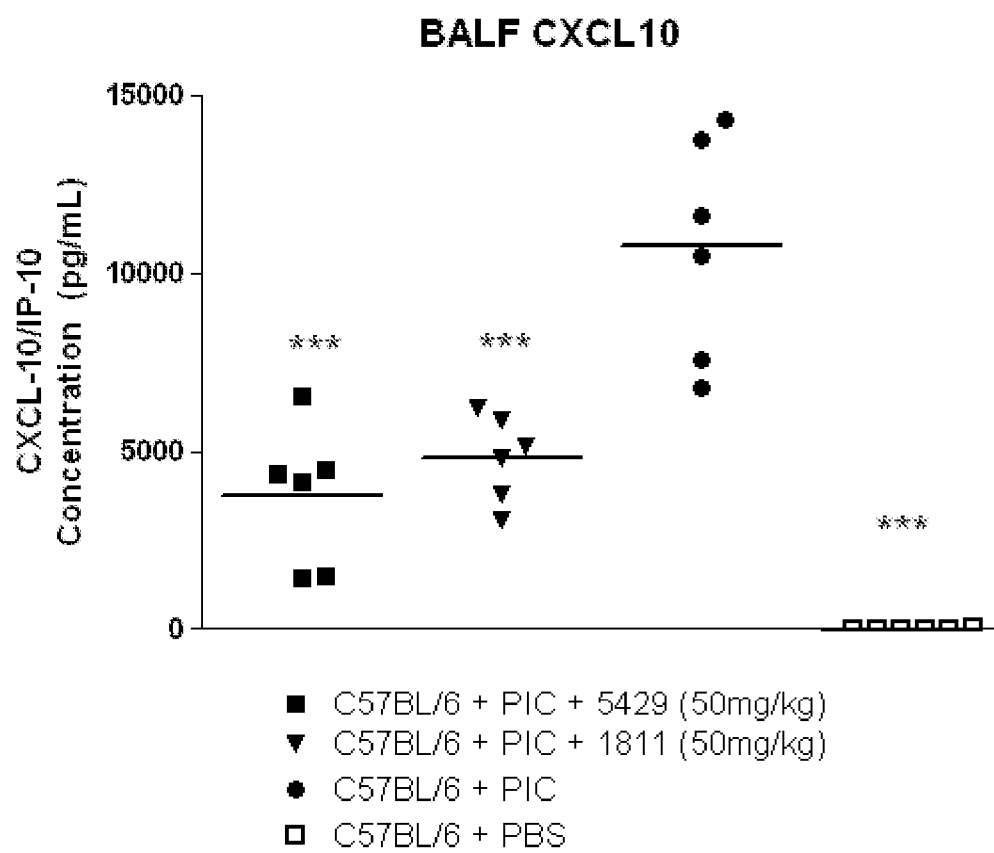
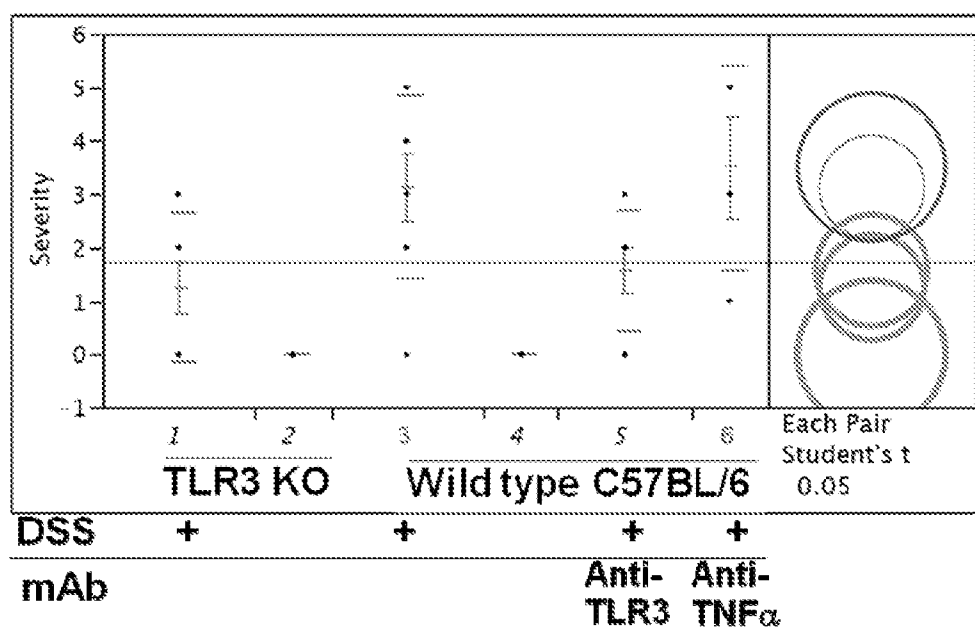


Figure 14



BLINDED scoring based on: Single cell necrosis, Epithelial ulceration, Epithelial sloughing, Cryptal abscess, Cryptal cell proliferation, LP Granulation tissue, Submucosal granulation tissue, Submucosal neutrophils, Submucosal edema

Figure 15

Figure 15A

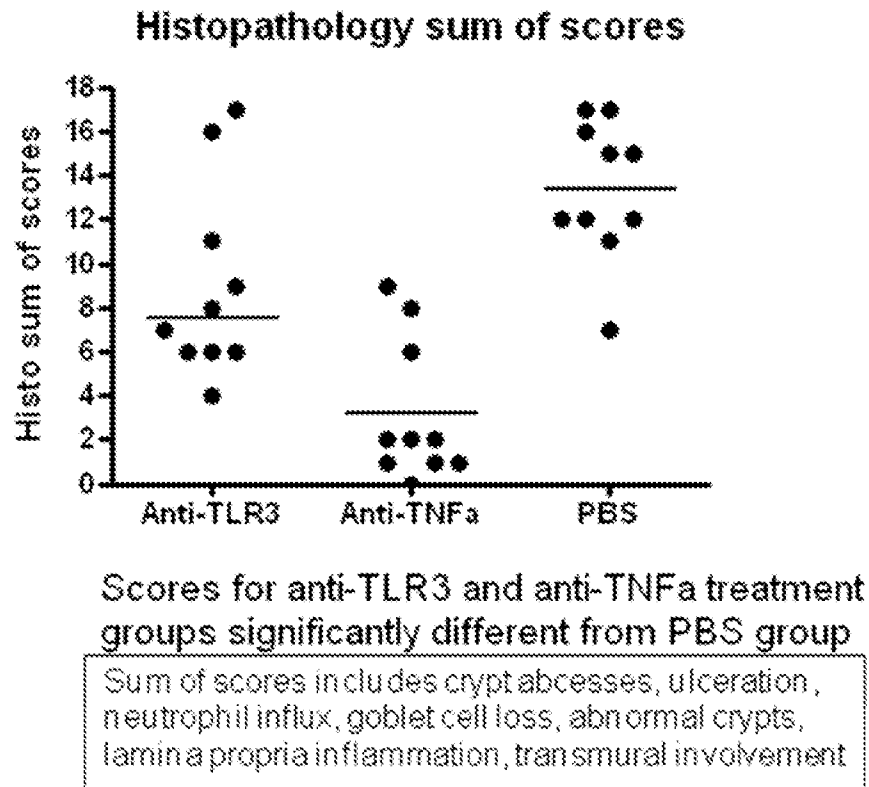


Figure 15B

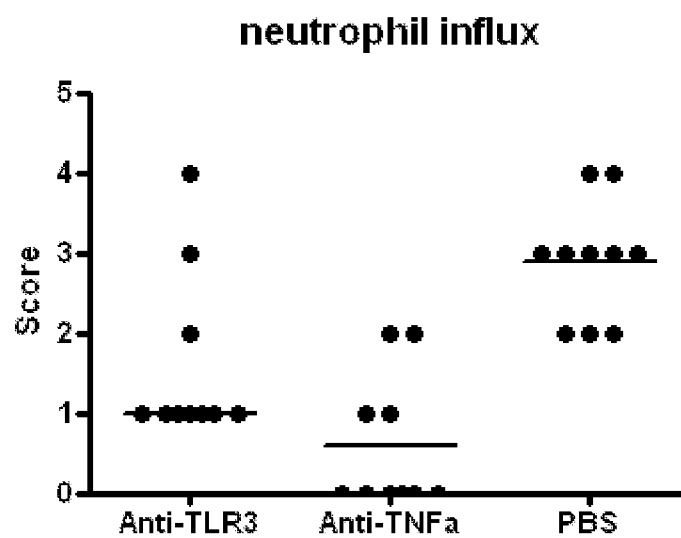


Figure 16

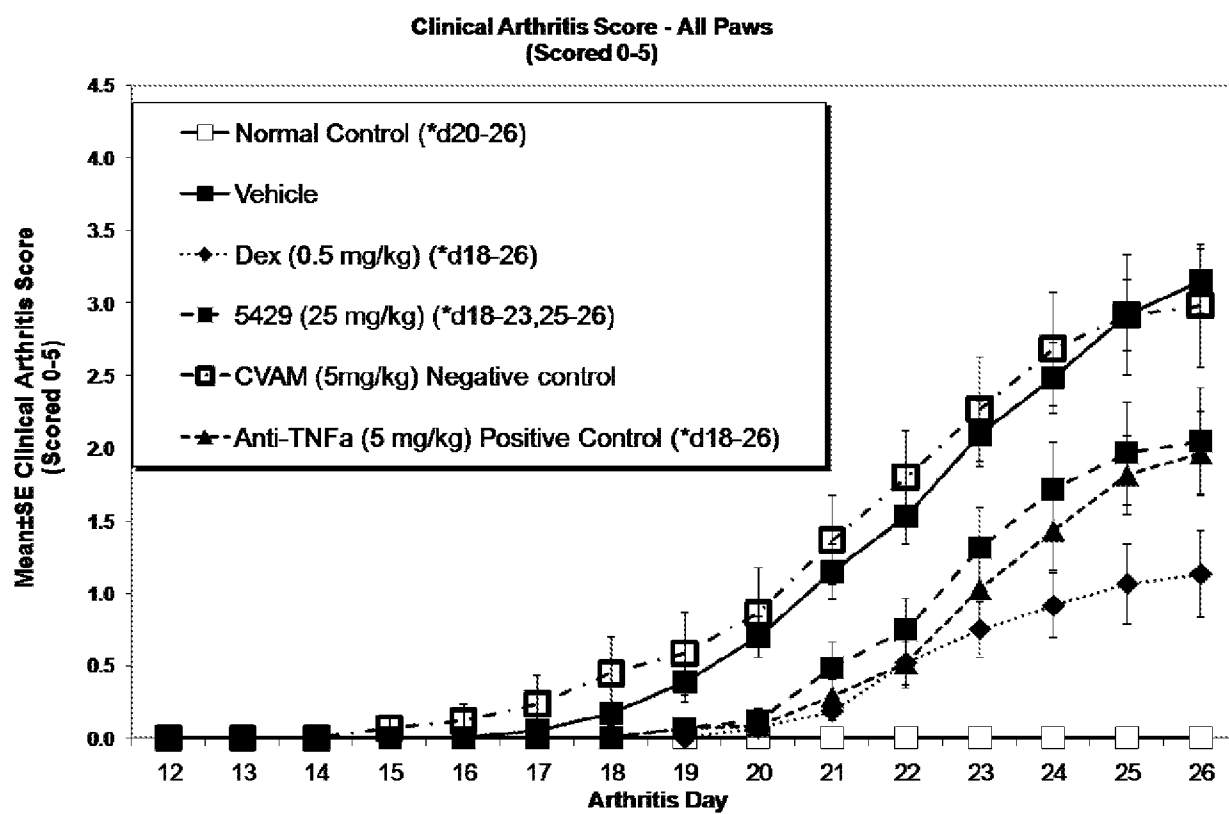


Figure 17

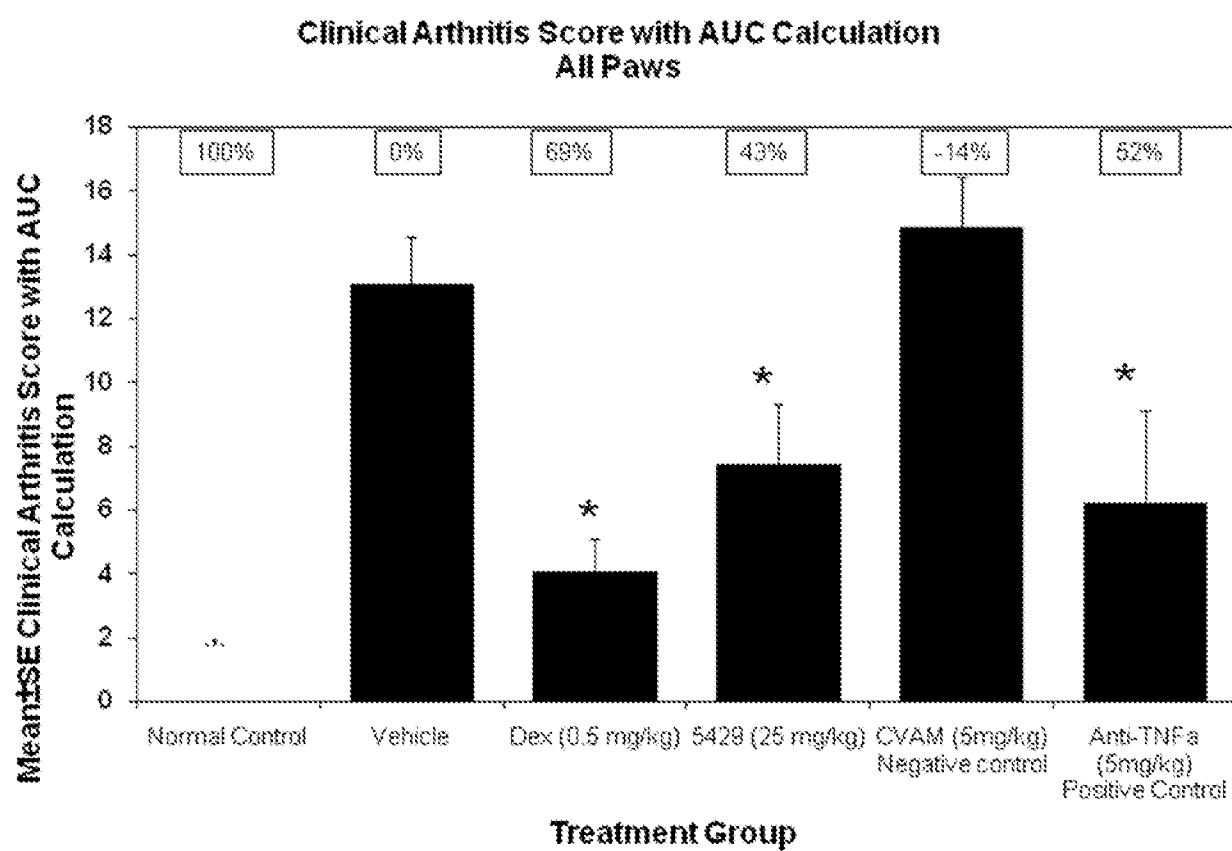


Figure 18

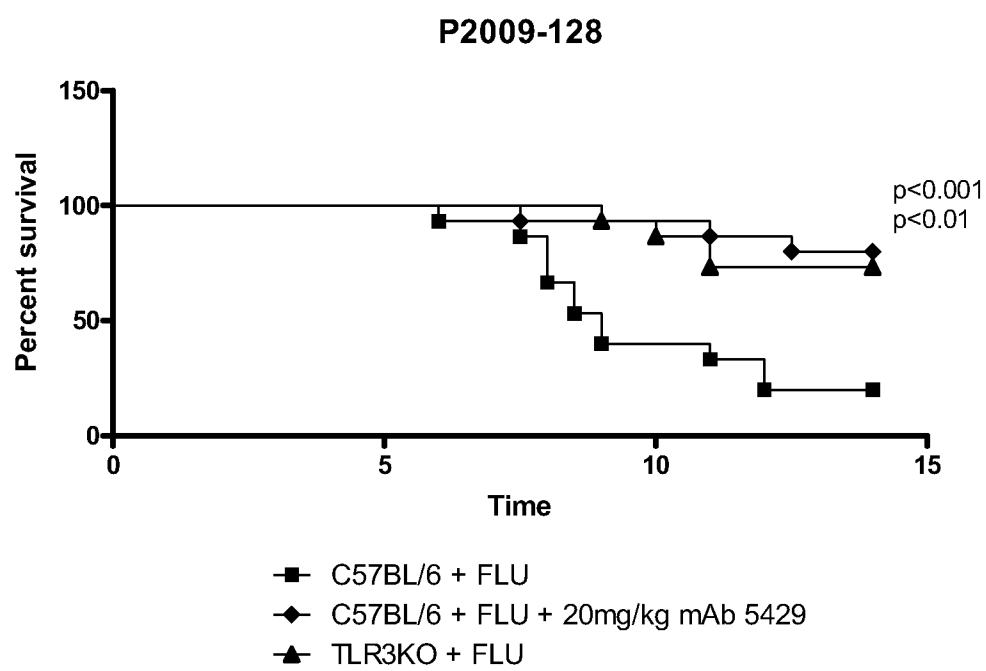


Figure 19

Clinical Score following administration of influenza A/PR/8/34.³

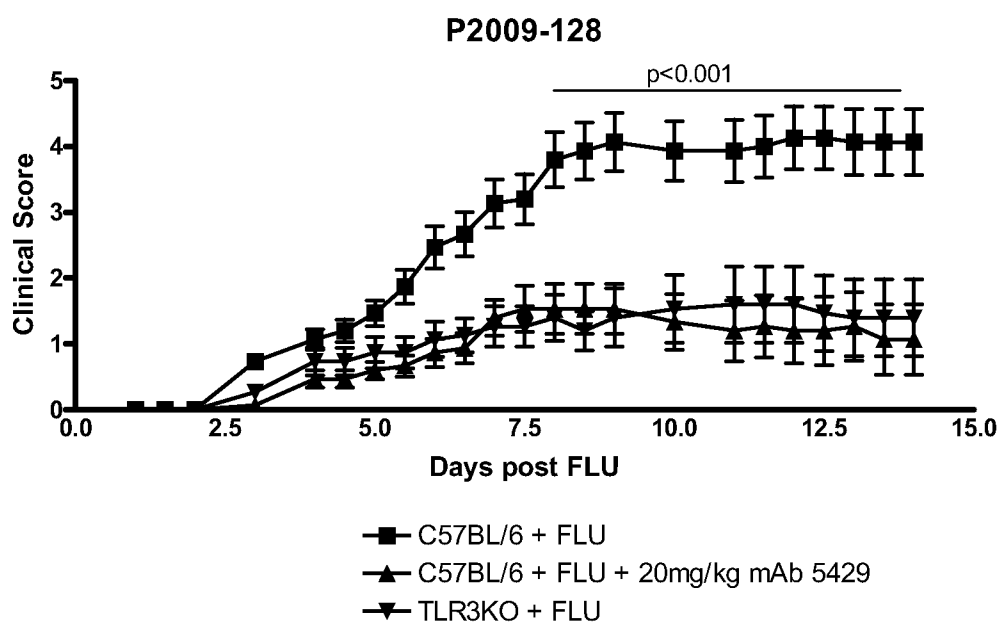
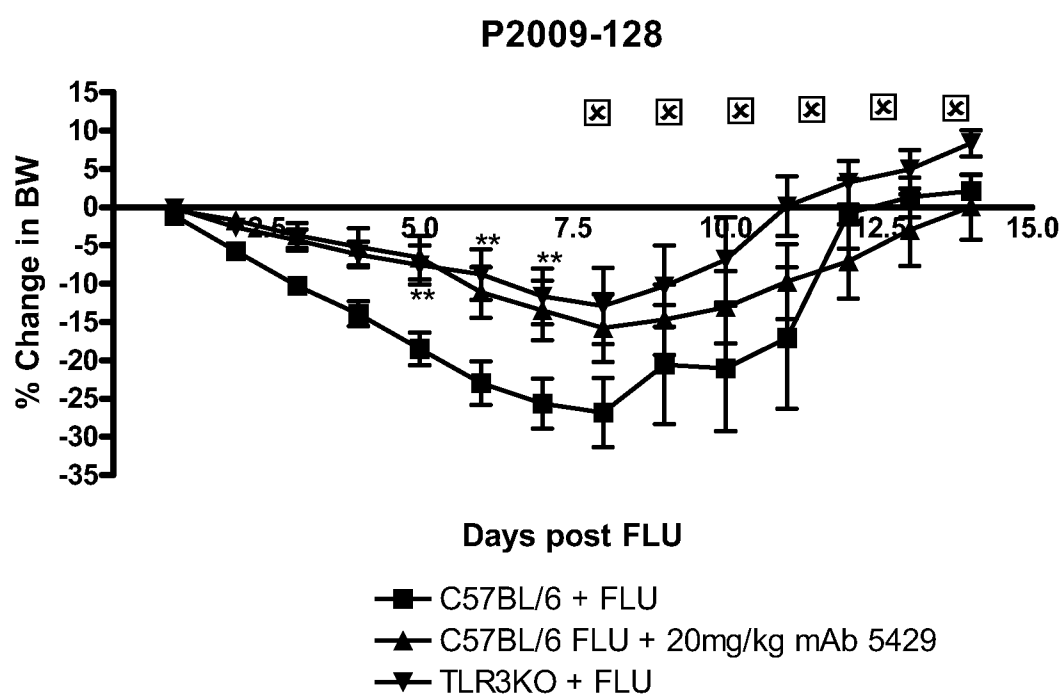


Figure 20



☒ Death of animals

Significant differences between mAb treated and KO groups vs. C57BL/6 +flu,
 $p < 0.01$ at day 5, 6, and 7

Figure 21

Figure 21A.

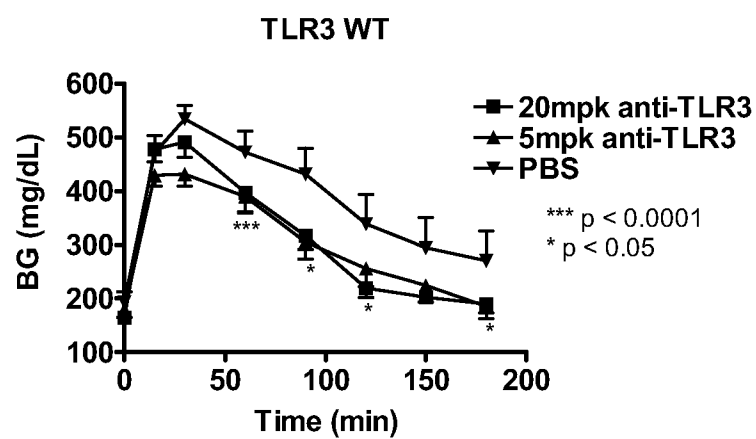


Figure 21B

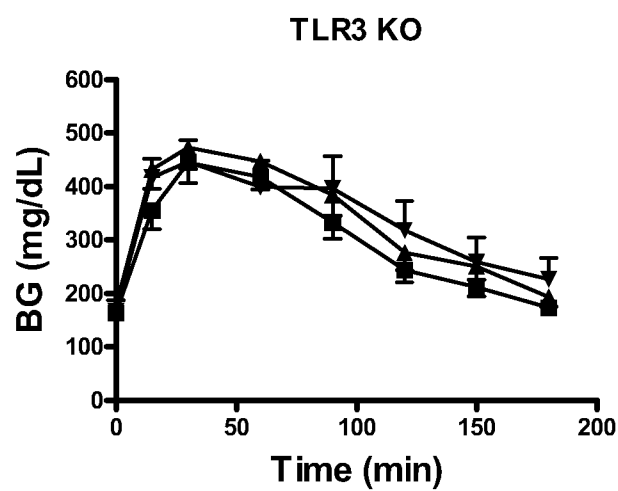


Figure 22

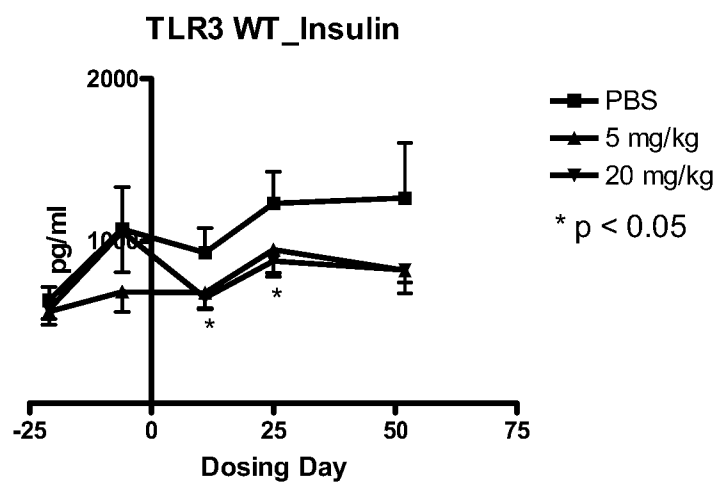


Figure 23

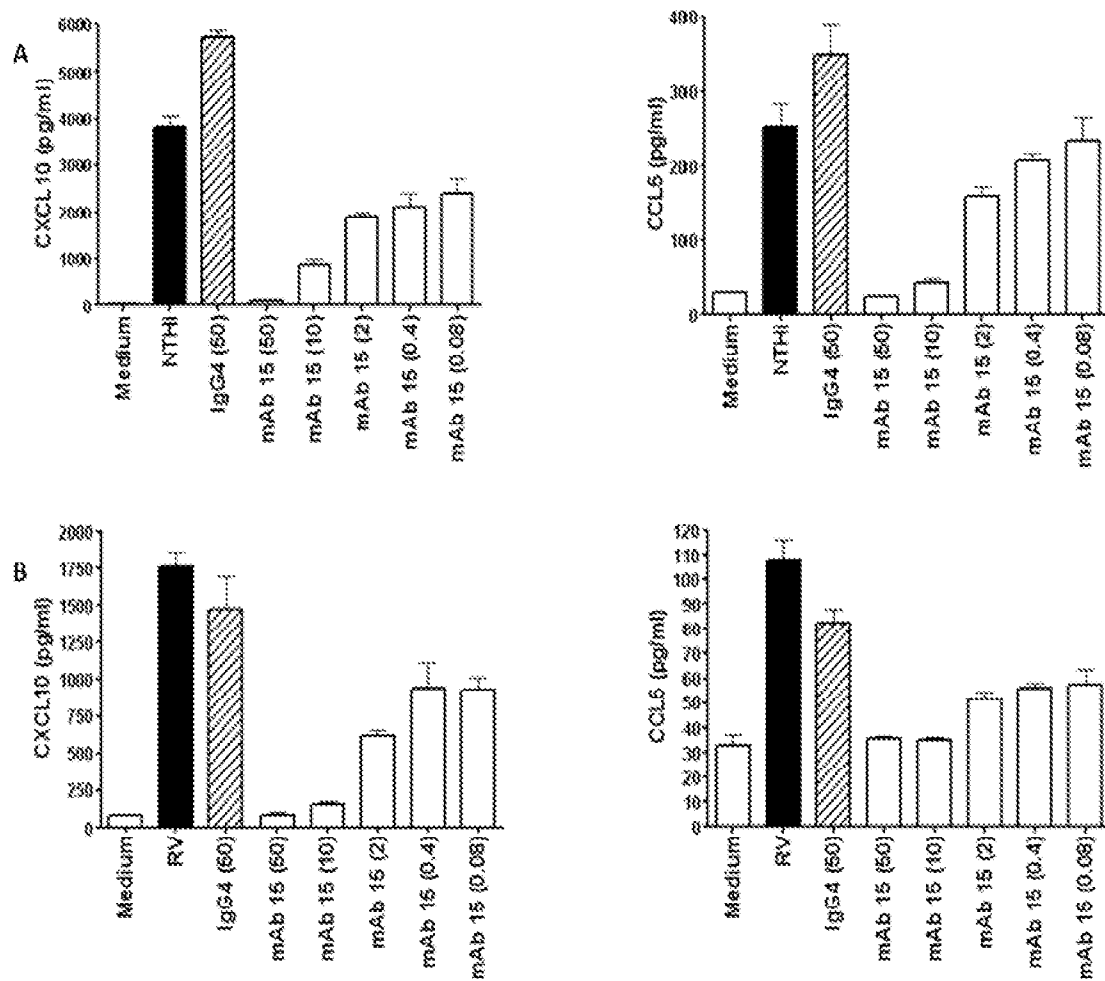
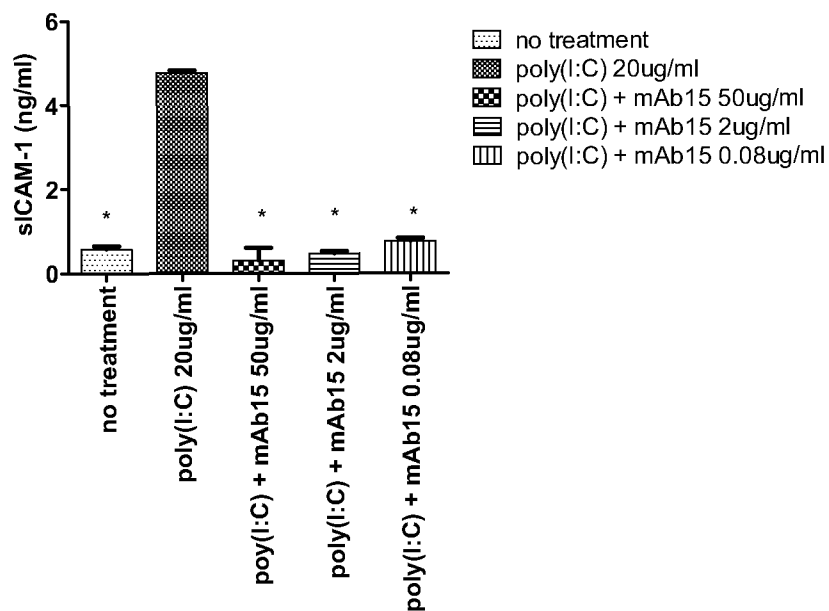


Figure 24

Figure 24A

mAb15 inhibits sICAM-1 in HUVECs stimulated with poly(I:C)

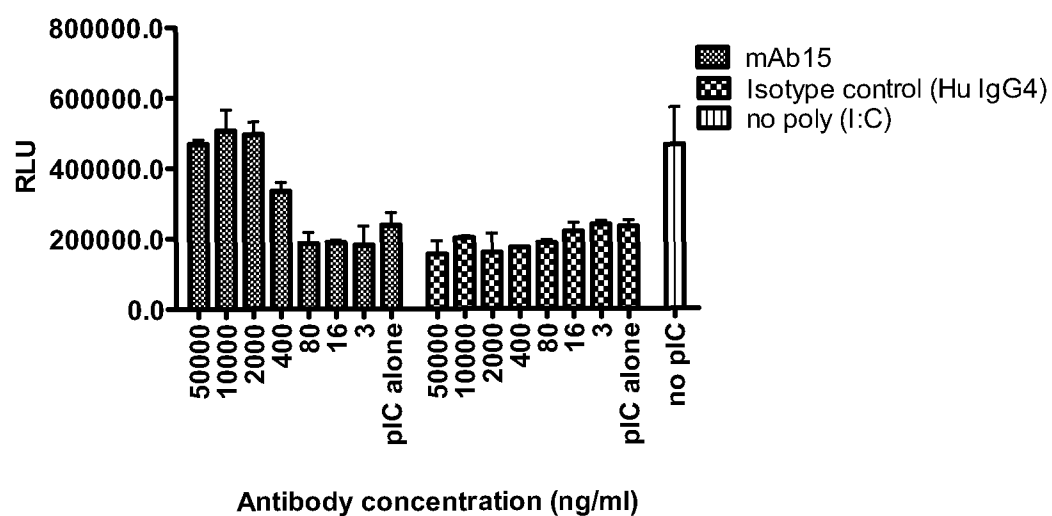


* mean values are significant ($p < 0.05$) vs. poly(I:C)

Endothelial cells stimulation

Figure 24B

Cell viability is restored by mAb15



REFERENCES CITED IN THE DESCRIPTION

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Szabadalmi igénypontok

1. Toll-like receptor-3-mal (TLR3-mal) reagálni képes izolált ellenanyag vagy fragmense, amely tartalmaz mind nehézlánc mind könnyűlánc variábilis régiót és ahol az ellenanyag tartalmazza a következőket:
 - a. a SEQ ID NO: 82, 86 és 84 szerinti nehézlánc CDR 1, 2 és 3 aminosav-szekvenciákat; and
 - b. a SEQ ID NO: 79, 80 és 87 szerinti könnyűlánc CDR 1, 2 és 3 aminosav-szekvenciákat.
2. Az 1. igénypont szerinti izolált ellenanyag vagy fragmens, amely tartalmazza a SEQ ID NO: 216 szerinti nehézlánc variábilis régiót és a SEQ ID NO: 41 szerinti könnyűlánc variábilis régiót.
3. Az 1. vagy 2. igénypont szerinti izolált ellenanyag vagy fragmens, amely tartalmazza a SEQ ID NO: 220 szerinti nehézláncot és a SEQ ID NO: 156 szerinti könnyűláncot.
4. Az 1-3. igénypontok bármelyike szerinti izolált ellenanyag vagy fragmens, ahol az ellenanyag rendelkezik legalább eggyel a következő sajátságok közül:
 - a. <1 µg/ml koncentráció esetén >50%-kal csökkenti a humán TLR3 biológiai aktivitását *in vitro* poli(I:C) NF-κB riportergén vizsgálati eljárással mérve;
 - b. <10 µg/ml koncentráció esetén >60%-ban gátolja a <100 ng/ml poli(I:C)-vel stimulált BEAS-2B sejtek IL-6 vagy CXCL10/IP-10 termelését;
 - c. <0,4 µg/ml koncentráció esetén >50%-ban gátolja a <100 ng/ml poli(I:C)-vel stimulált BEAS-2B sejtek IL-6 vagy CXCL10/IP-10 termelését;
 - d. <5 µg/ml koncentráció esetén >50%-ban gátolja a 62,5 ng/ml poli(I:C)-vel stimulált NHBE sejtek IL-6 termelését;
 - e. <1 µg/ml koncentráció esetén >50%-ban gátolja a 62,5 ng/ml poli(I:C)-vel stimulált NHBE sejtek IL-6 termelését;
 - f. <1 µg/ml koncentráció esetén >20%-ban gátolja a PBMC poli(I:C)-vel stimulált IFN-γ, IL-6 vagy IL-12 termelését;
 - g. <10 µg/ml-es IC50 értékkel gátolja a Cynomologus TLR3 biológiai aktivitását *in vitro* NF-κB riportergén vizsgálati eljárással mérve; vagy
 - h. <5 µg/ml-es IC50 értékkel gátolja a Cynomologus TLR3 biológiai aktivitását *in vitro* ISRE riportergén vizsgálati eljárással mérve.
5. Az előző igénypontok bármelyike szerinti izolált ellenanyag vagy fragmens, ahol
 - a. az ellenanyag teljesen humán;
 - b. az ellenanyag vagy fragmens humán-adaptált;
 - c. az ellenanyag polietilén-glikolhoz van konjugálva; vagy
 - d. az Fc domén tartalmaz S229P, P235A vagy L236A mutációt.
6. Az előző igénypontok bármelyike szerinti izolált ellenanyag vagy fragmens amely IgG4 izotípusú.
7. Az előző igénypontok bármelyike szerinti izolált ellenanyagot vagy fragmenst és gyógyászati lag elfogadható hordozót tartalmazó gyógyászati készítmény.

8. Az 1-6. igénypontok bármelyike szerinti izolált ellenanyag vagy fragmens vagy a 7. igénypont szerinti gyógyászati készítmény, terápiás alkalmazásra.

9. Az 1-6. igénypontok bármelyike szerinti izolált ellenanyag vagy fragmens vagy a 7. igénypont szerinti gyógyászati készítmény a következők bármelyikének kezelésében történő alkalmazásra:

- a) gyulladásos rendellenesség, ahol adott esetben a gyulladásos rendellenesség:
 - i) a következőkből álló csoportból kiválasztott szövetet érinti: légúti-, tüdő-, gasztrointesztinális, vékonybél-, vastagbél-, kolon-, végbél-, kardiovaszkuláris rendszeri, szív-, véréreny-, ízületi, csont- és szinoviális, porc-, epitel-, endotél-, máj- és zsírszövet;
 - ii) összefüggésben áll a szövetbe történő fokozott TLR3-mediált neutrofil infiltrációval;
 - iii) gyulladásos tüdő-rendellenesség, adott esetben:
 - I) asztma vagy krónikus obstruktív tüdőbetegség (COPD);
 - II) atípusos Haemophilus influenza által indukált; vagy
 - III) légúti hiperreszponzivitás, adott esetben asztmával, allergiás rinitisszel, COPD-vel vagy cisztás fibrózissal asszociált;
 - iv) gyulladásos bélbetegség;
 - v) gasztrointesztinális fekélyel asszociált, adott esetben fertőző kolitisszel, iszkémiás kolitisszel, kollagén vagy limfocitás kolitisszel vagy nekrotizáló enterokolitisszel; vagy
 - vi) autoimmunbetegség, adott esetben reumás.
- b) II. típusú cukorbetegség;
- c) hiperglikémia; vagy
- d) hiperinzulinémia;

ahol az eljárás magában foglalja az izolált ellenanyag vagy fragmens vagy a gyógyászati készítmény terápiásan hatásos mennyiségének beadását arra rászoruló páciensnek annyi időn keresztül, ami elégséges a gyulladásos rendellenesség, II. típusú cukorbetegség, hiperglikémia vagy inzulin rezisztencia kezelésére vagy megelőzésére.

10. Az 1-6. igénypontok bármelyike szerinti izolált ellenanyag vagy fragmens vagy 7. igénypont szerinti gyógyászati készítmény a következők kezelésére vagy megelőzésére szolgáló eljárásban történő alkalmazásra:

- a) szisztémás gyulladásos rendellenesség, adott esetben citokinvihar vagy hipercitokinémia, szisztémás gyulladásos válasz szindróma (SIRS), graft-versus-host betegség (GVHD), akut légúti distressz szindróma (ARDS), súlyos akut légúti distressz szindróma (SARS), katasztrofális anti-fosfolipid szindróma, súlyos vírusos fertőzés, influenza, tüdőgyulladás, sokk, vagy szepszis; vagy
- b) vírusos fertőzés, adott esetben influenza A vírus általi fertőzés;

ahol az eljárás magában foglalja az izolált ellenanyag vagy fragmens vagy a gyógyászati készítmény terápiásan hatásos mennyiségének beadását arra rászoruló páciensnek annyi időn keresztül, ami elégséges a szisztémás gyulladásos rendellenesség vagy vírusos fertőzés kezelésére vagy megelőzésére.

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